DIRECT COMPRESSION SUITABILITY OF OLMESARTAN MEDOXOMIL AND AMLODIPINE BESYLATE USING SEDEM DIAGRAM

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IN

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By

(Reg No: 261510403)

Under the guidance of

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CERTIFICATE

This is to certify that the investigation described in this dissertation entitled **DIRECT COMPRESSION SUITABILITY OF OLMESARTAN MEDOXOMIL AND AMLODIPINE BESYLATE USING SEDEM DIAGRAM** Submitted by Reg No: 261510403 was carried out in the Department of Pharmaceutics, Arulmigu Kalasalingam College Of Pharmacy, Anand Nagar, Krishnankoil-626126, Which is affiliated to The Tamilnadu Dr.M.G.R.Medical University, Chennai, under the supervision and guidance of **Dr.J.JEYA ANANTHI, M.Pharm, Ph.D.,** Professor, Department of Pharmaceutics for the partial fulfillment of the degree of MASTER OF PHARMACY in PHARMACEUTICS , Arulmigu Kalasalingam College of Pharmacy, Anand Nagar , Krishnankoil-626126

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EVALUATION CERTIFICATE

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Examiners:

1.

2.

DEDICATED TO GOD , MY FAMILY AND FRIENDS

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"**You will meet more angels on a winding path than on a straight one"**

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CONTENT

INDEX


INTRODUCTION

INTRODUCTION

Direct compression (DC) is the simplest means of production of a pharmaceutical tablet. It requires only that the active ingredient is accurately blended with suitable excipients previous to compression. A part from the simplicity of formulation and manufacture, the key in advantages of direct compression contain reduced capital, labor, and force costs for manufacture and the escaping of water for granulation for water responsive drug substances. This guide describes the scope and first principles involved in the formulation of tablets by direct compression. The most observable part in determining whether DC is related to a certain drug substance is dose. Three key factors for successful tab letting are flow and the compressed facility of the compression mix up, and drug content uniformity in the blend and the final tablets. All of these factors are likely to be affect by drug dose. In this lead, a low dose is in use to mean 10 mg or lower, the medium dose is taken to mean 10 mg to 50 mg and high dose is taken to mean above 50mg.For low dose drugs, flow and compaction of the compression mix are largely confer by the excipients and the primary concern is likely to getting of good content uniformity in the blend and in the tablets. For medium dose drugs flow of the compression mix may become a vital factor, and for high dose drugs the flow and compaction are highly dependent on the property of the drug substance [1]

Advantages and Disadvantages Of Direct Compression:

Advantages

• Fewer stability issues for actives that are sensitive to heat or moisture

• For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, norfloxacin

• Fewer excipients may be needed in a direct compression formula

Disadvantages

• Issues with segregation – these can be reduced by matching the particle size and density of the active drug substance with excipients

• In general, the drug content is limited to approximately 30% or approximately50 mg

• May not be applicable for materials possessing a low bulk density since after compression the tablets produced may be too thin

• Not proper for poorly flowing drug compounds

• Static charge may develop on the drug particles or excipients during mixing, which can guide to agglomeration of particle produce poor mixing

Direct Compression Excipients

Although the principles leading direct compression have been well known for many years, the method has only recently grown to be more establish as a result of the introduction of excipients specially designed for direct compression. These excipients are not only directly compressible themselves, but can also be mix with a large proportion of drug substance with no major corrosion in tablet quality. In to excipients possessing good flow and compression property, they must also possess the following attributes

• Particle size distributions to are similar to most active drug substances, thus avoid separation during processing

• A high bulk density;

• The batch-to-batch value must be reproducible. These attributes are the most dangerous for direct compression functionality. The remaining attribute are necessary for all excipients

• Physically and chemically constant when in getting in touch with moisture, air and heat

• Chemically inert; do not enhance the degradation of active ingredients or other excipients

• Compatible with covering works

• Available international, and rather from more than one supplier.

For example, microcrystalline cellulose can be used as an anti-adherent (5–20%), a disintegrant (5–15%) and the same as diluents (20–90%). material that is currently available as direct compression vehicles can be classified according to their fail with flow property

Disintegrant and Poor Flow of Microcrystalline Cellulose

Microcrystalline cellulose is a purify partially depolymerized cellulose, which is ready by treat a-cellulose with mineral acids, produce bundles of needle-like microcrystal. In expressions of appearance, this excipient is a white, crystalline powder composed of agglomerated porous particles. In a survey conduct by the pharmaceutical industry, Shang raw and Demarest finished that several formulation scientists rank microcrystalline cellulose as the majority useful filler for direct compression. Its regard can be credited to its excellent compactibility at low pressures, high dilution possible and greater disintegration properties. Eg; paracetamol and potassium phenethicillin as model compounds.

Starch 1500

Local starches cling to good compression individuality, except their poor flow properties and far above the ground lubricant sensitivity perform construct them a smaller amount suitable for use in direct compression. They are mostly useful as a result of their good binding and disintegrant properties. Nevertheless, Starch 1500 continues to be widely regarded as the after that choice excipient before lactose and microcrystalline cellulose. Starch 1500 is a form of pregelatinized starch that has been modified to create it extra compressible and flow able in character. In conditions of look, it is a white to an off-white powder of a more or less coarse-to-fine nature. It is odorless but is report to have a unique taste. During the manufacturing process, a little of the hydrogen bonding among amylose and amylopectin is partially rupture, so that the product contain 5% free amylose, 15% free amylopectin and 80% unchanged starch. The free amylose is dependable for the disintegration property and the free amylopectin provides cold water solubility and aids the binding property. Starch 1500 is very sensitive to the softening property of alkaline separate lubricants. For this reason, the use of magnesium stearate is supposed to be avoided or kept at a level below 0.5% since higher concentration can have adverse effects on tablet strength and dissolution. Consequently, stearic acid is typically preferred as the lubricant to be used with pregelatinized starch. Starch is a good disintegrant but this property may cause longer-term problems because the compacts formed may be friable. At high strain rates during

compression, a large amount of the bend is a stretch and therefore, extend recovery occurs during the act of exclusion, remind cap.

The Sedem expert system is a methodology which is useful in preformulation and formulation study of medicines mostly in solid dosage forms. This system inform on the physical shape of powdered substances (APIs and excipients) used to formulate drugs.[2] By influential whether powders (API or excipients) are proper used for direct compression, the SeDeM summary will inform about the advantages and gap of that powdered substance to be used in direct compression, so the system inform on whether the direct compression method is suitable (e.g.. wet granulation should be applied before compression).This novel method is based on the selection and application of some parameters that the formulation should fulfill to make sure a booming tablet elaborate by direct compression. The following principle is applied

Parameters Examined By the SeDeM Method:

SeDeM uses 12 tests [3] to examine whether a powder is suitable for direct compression.

- Bulk density (Da)
- Tapped density (Dc)
- Inter-particle porosity (Ie)
- Carr index (IC)
- Cohesion index(Icd)
- Hausner ratio(IH)
- Angle of repose(α)
- Flowability (t″)
- Loss on drying (%HR)
- Hygroscopicity (%H)
- Particle size (%Pf)
- Homogeneity index (Iθ)

These tests are grouped into five factors on the basis of the physical characteristics of the powder and the functionality of the drug:

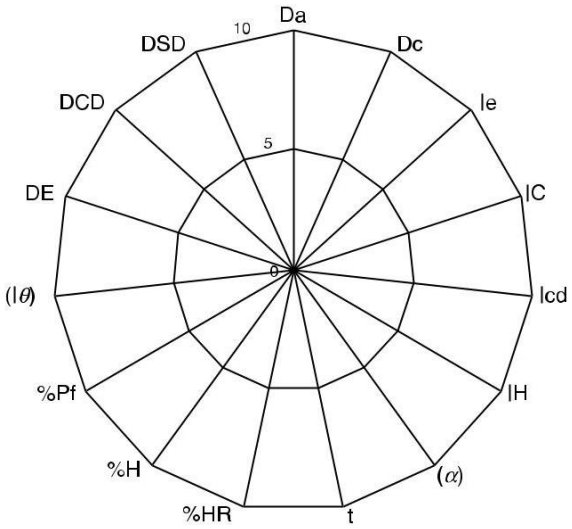
- Dimensional Parameter
- Compressibility Parameter
- Flow ability/Powder Flow Parameter
- Lubricity/Stability Parameter
- Lubricity/Dosage parameter.

Table no: 1.1 these tests are grouped into five factors on the basis of the physical characteristics of the powder and the equation:

INCIDENCE FACTOR	PARAMETER	SYMBOL	UNIT	EQUATION
Dimension	Bulk Density	Da	g/ml	Da = P/Va
	Tapped Density	Dc	g/ml	Dc = P/Vc
Compressibility	Inter-particle Porosity	Ie	-	Ie = Dc − Da/Dc × Da
	Carr Index	IC	%	IC = (Dc − Da/Dc) 100
	Cohesion Index	Icd	N	Experimental
Flowability/Powder Flow	Hausner Ratio	IH	-	IH = Dc/Da
	Angle of Repose	(α)	°	tg α = h/r
	Powder Flow	t″	s	Experimental

Lubricity/Stability	Loss on Drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/Dosage	Particles < 50 µm	%Pf	%	Experimental
	Homogeneity Index	(Iθ)	-	* Iθ = Fm / 100 + Δ Fmn

The SeDeM method is also a helpful device for the study of the reproducibility of a manufacturing method used for a powdered substance and, therefore of the validation of systematic variation in explanation. A manufacturing process gives increase to variations in the last product and these variations should fall within limits or traditional specifications, by applying the SeDeM method to study reproducibility involving batch of the same API or excipient, specifications in the different parameters can be established to make assured the same quality of the product regardless of the batch analyze. In adding up, these specifications must be used for the establishment of particular limits for value manages the application. To achieve this target it is necessary to study the parameters of the SeDeM Diagram, applying the similar statistic analyses required to set up the SeDeM Diagram: A New Expert System for the Formulation of Drugs in Solid Form 31 pharmaco technical uniformity between batches. Correct reproducibility between batches will ensure the reproducibility and the worth of the tablets formulated with this API or excipient, apart from of the batch used. SeDeM Diagrams of three batches from the same API, In this case, the mark and the index were very similar. This control has the advantage that the procedure has the capacity to detect variations in particle size between batches of the product. This ability, in consequence, contributes to the formulation of the pharmaceutical forms and their correct dissolution the formulation must be representative and appropriate for the supplies of compression technology. The implementation of the experimental methodology and calculus must be willingly relevant.



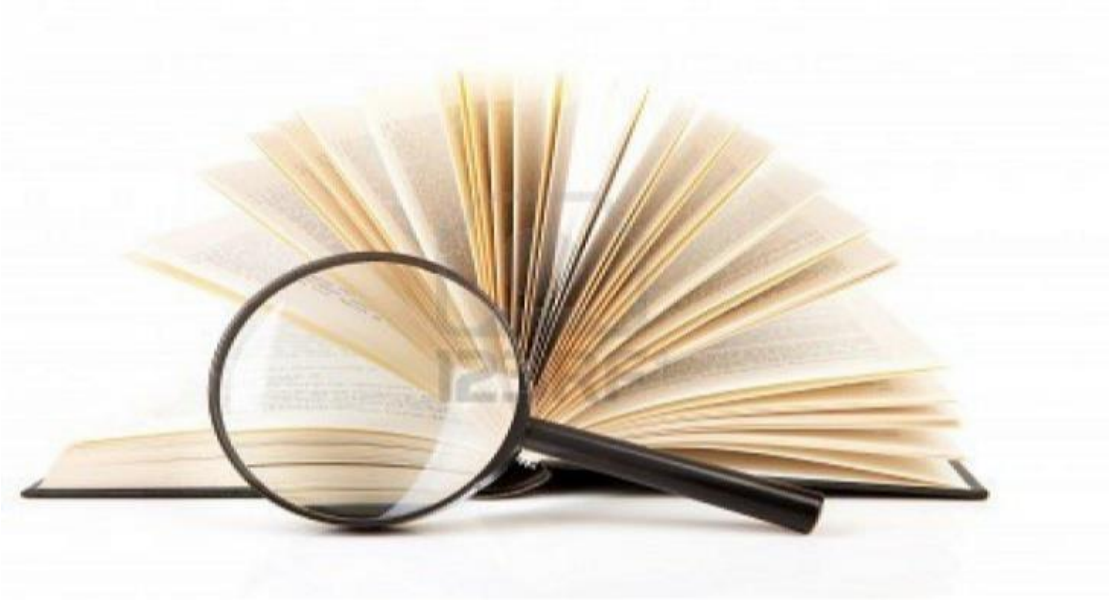
The SeDeM diagram is a novel and reproducible method for application to preformulation studies of tablets [4]. The suitability of a powder (active or inactive pharmaceutical ingredient) for direct compression can be studied using this method. Moreover, this method can be seen as a useful tool for studying the reproducibility of a method used for the preparation of powdered substance. Certain powder characteristic parameters are taken into concern for the development of SeDeM diagram. These selected parameters are consequently studied and analyze statistically to determine the applicability of the method. Also, to ensure reproducible powder quality, suitable specifications are recognized for different classification parameters. These specifications should also be used to set an acceptable range for each parameter adopted in unity with the SeDeM method, with the aim of providing valid specifications for any powder substance concerning its suitability for direct compression [5, 6]. The SeDeM method is based on the experimental study and quantitative determination of the characterization parameters of powdered substances that provide the necessary information about the ability of a substance to be used for direct-compression technology. These 12 parameters were determined by validated experimental methods and processed for fitting into SeDeM diagram method and analyze for studying the suitability of the powder for direct compression. Thus, SeDeM diagram method could be described as a mathematical and graphical representation of powder point parameters

for learning direct compression appropriateness of different active and inactive ingredients

Determination of acceptable limit values for each parameter included by the SeDeM method:

have achieved the values as described more than, certain limits are set on the basis of the parameters selected and the values described in the exercise manual of Pharmaceutical Excipients or alternatively on the center of experimental tests.

S NO.	INCIDENCE	PARAMETER	ACCEPTABLE RANGE
1	Dimension	Bulk density	0–1 g/ml
		Tapped density	0-1 g/ml
2	Compressibility	Inter-particle porosity	0–1.2
		Carr index	0–50 (%)
		Cohesion index	0–200 (N)
3	Flow ability/powder flow	Hausner ratio	3–1
		Angle of repose	50–0 (°)
		Powder flow	20–0 (s)
4	Lubricity/stability	Loss on drying	0-10 (%)
		Hygroscopicity	20–0 (%)
5	Lubricity/dosage	Particles < 50 μ	50–0 (%)
		Homogeneity index	0–2 × 10−2



Literature Review

LITERATURE REVIEW

Josep M. Sune-Negre, et al, Analyzed Application of the new SeDeM Method is proposed for the study of the galenic properties of excipients in terms of the applicability of direct-compression technology. Through experimental studies of the parameters of the SeDeM Method and their subsequent mathematical treatment and graphical expression (SeDeM Diagram), six different DC diluents were analyzed to determine whether they were suitable for direct compression (DC). Based on the properties of these diluents, a mathematical equation was established to identify the best DC diluents and the optimum amount to be used when defining a suitable formula for direct compression, depending on the SeDeM properties of the active pharmaceutical ingredient (API) to be used. The results obtained confirm that the SeDeM Method is an appropriate system, effective tool for determining a viable formulation for tablets prepared by direct compression, and can thus be used as the basis for the relevant pharmaceutical development. [8]

Johnny Edward Aguilar-Dıaz et al, Studied the SeDeM expert system is based on the experimental study and quantitativedetermination of the characterization parameters of powdered substances, the aim being to determine whether a substance is suitable for producing tablets by means of direct compression (DC) technology, thereby reducing the lead time for pre-formulation studies. Additionally, this expert system also provides formulations with a minimum number of excipients.We used this system to analyze suitable formulas for the production of oro dispersible Ibuprofen tablets. Twenty-one disintegrants and ibuprofen were characterized using SeDeM methodology. The results indicated that production of ibuprofen tablets by DC would require improvements in the dimension and compressibility factors of the active pharmaceutical ingredient. The expert system analysis provided the specific percentage of disintegrant needed to blend with ibuprofen and a standardized formula of lubricants in order to obtain a powder mix that would successfully produce tablets by DC. The eight formulas proposed by SeDeM were produced and tested in the laboratory. All

eight formulas successfully produced tablets by DC, but only four of them could be considered suitable for use as an orodispersible tablet and accomplishes all the pharmaceutical quality parameters. So, in fact, the use of the SeDeM system reduced the time of medicine's development and therefore the cost of the activity. [9]

Johnny Edward Aguilar-Díaz, et al, examined the new SeDeM Diagram expert system was used to analyze the suitability of 43 excipients for direct compression with disintegrating properties from eight chemical families. The SeDeM Diagram expert system is a new method for use in tablet preformulation and formulation studies. It provides the profile of a substance in powder form in terms of its suitability for direct compression. This study was based on the current concept ''Quality by Design ICH Q8". In this the pharmacotechnicalproperties of disintegrants were evaluated in powder form and selected the candidates that were most suitable for direct compression and their use in the formulation of orally disintegrating tablets (ODT). To achieve this, each disintegrant and its chemical families were individually analyzed. It was concluded that nine disintegrants had a SeDeM value with the index of good compression (IGC) over 5. Most of these disintegrants were from the micro cellulose family. Other disintegrants had indexes that were close to 5. It is assumed that these excipients can be used in direct compression when they are added to other excipients. [10]

Josep M. Suñé-Negre, et al, performed as a methodology for characterizing substances in relation to their viability in direct compression, the SeDeM Diagram Expert System may be considered an open system in terms of the number of parameters applied and the optimization of these parameters. With the experience acquired from applying the SeDeM Diagram, in this study, we propose optimizing the parameters corresponding to the Hausner index (IH) and relative humidity (%HR) in order to simplify the mathematical calculation, so that it provides reliable data that can be extrapolated. The proposed optimization does not involve a conceptual change in the parameters considered nor did a significant change in the results obtained to compare with the previous calculation methodology initially established for the SeDeM Diagram Expert System, which means that the conclusions obtained by applying this method are equivalent. [11]

Johnny Edward Aguilar, et al, evaluated SeDeM-ODT expert system is an innovative tool for predicting whether or not an excipient or mixture of powders containing API and excipients is suitable to obtain a buccal dispersible tablet by direct compression. This preformulation tool identified as the index of good compressibility and Oro dispersibility (IGCB index), unique to each powder or mixture of powders and based on the SeDeM expert system. The IGCB index indicates if a mixture of powder can be compressed by direct compression and, at the same time, indicates if the resulting tablets would be suitable for use as orodispersible tablets. SeDeM ODT and SeDeM expert systems are excellent tools to optimize tablet fabrication. These tools allow a reduction in the number of unnecessary experiments in the laboratory because they provide information on rheology, compatibility properties, etc. In addition, these tools also provide information that can be used for a better understanding of the formulation design. [12]

Sherine S. Diab,e tal prepared Spectrophotometric methods for simultaneous determination of a ternary mixture of amlodipine besylate, olmesartanmedoxomil, and hydrochlorothiazide. Four, accurate, precise, and sensitive spectrophotometric methods are developed for the simultaneous determination of a ternary mixture amlodipine besylate (AM), olmesartan medoxomil (OL) and hydrochlorothiazide (HZ), where AM is determined at its ʎ max 364.6 nm (0D), while (OL) and (HZ) are determined by different methods. Method (A) depends on determining OL and HZ by measuring the second derivative of the ratio spectra (2DD) at 254.4 and 338.6 nm, respectively. Method (B) is first derivative of the double divisor ratio spectra (D-1DD) at 260.4 and 273.0 nm for OL and HZ, respectively. Method (C) based on successive spectrophotometric resolution technique (SSRT). The technique starts with the ratio subtraction method then measuring OL and HZ at their isoabsorption point at 260.0 nm, while HZ is measured using the amplitude of the first derivative at 335.2 nm. Method (D) is mean centering of the ratio spectra (MCR) at 252.0 nm and 220.0 nm for OL and HZ, respectively. The specificity of the developed methods is investigated by analyzing laboratory prepared mixtures containing different ratios of the three drugs and their combined dosage form.The obtained results are statistically compared with those obtained by the official

or reported methods, showing no significant difference with respect to accuracy and precision at p = 0.05.[14]

Bindi N. Vora et al, performed Development and validation of the simultaneous UV spectrophotometric method for estimation of metoprolol succinate and olmesartan medoxomil in the tablet dosage form. The linearity was obtained in the concentration range of5–25 µg/ml and 4–20 µg/ml for METO and OLME, respectively. The concentrations of the drugs were determined by using the simultaneous equations method. The mean recovery was 100.90 ± 1.76 and 100.26 ± 0.71 for METO and OLME, respectively. The method was found to be simple, accurate, and precise and was applicable for the simultaneous determination of METO and OLME in the pharmaceutical tablet dosage form. The results of analysis have been validated statistically and by recovery studies. [15]

Anjali Patel et al, carried out the development of the UV spectrophotometric method of Olmesartanmedoxomil in bulk drug and pharmaceutical formulation and stress degradation studies. A simple, sensitive, specific, spectrophotometric method was developed for the detection of Olmesartanmedoxomil (OLM) in bulk and pharmaceutical formulations. The optimum conditions for the analysis of the drug were established. OLM was subjected to stress degradation under different conditions recommended by the International Conference on Harmonization (ICH). The samples so generated were used for degradation studies using the developed method. The λmax of the OLM was found to be 257 nm. The method exhibited high sensitivity, with linearity, in the 2 to 20 µg/ml range. The lower limit of detection and the limit of quantification were found to be 1.012 µg/ml and 3.036 µg/ ml, respectively. All the calibration curves demonstrated a linear relationship between the absorbance and concentration, with the correlation coefficient higher than 0.99. The regression equation of the curve was Y = 0.0579x + 0.0006. The precision of the method was found to be 40.043 ± 0.067 against the label claim of 40 mg. The percentage recovery was found to be 101.32 ± 0.452. The sample solution was stable for up to two hours. Hence, it could be concluded that the proposed method would be suitable for the analysis of OLM in bulk and pharmaceutical formulations. [16]

Kun-Yan Li, et al, performed the Relative Bioavailability and Fasting Pharmacokinetics of Three Formulations of OlmesartanMedoxomil 20-mg Capsules and Tablets in Healthy Chinese Male Volunteers: An OpenLabel, Randomized-Sequence, Single-Dose, Three-Way Crossover Study, Twenty-one healthy male subjects (mean age, 21 years [range, 18-25 years]; weight, 62.1 kg [range, 54.0-80.0 kg]) were enrolled in and completed the study. No period or sequence effect was observed. The mean AUCo_=values for the test tablet, test capsule, and reference tablet were 3993 (1070),3567 (850), and 3849 (872) ng/mLlh, respectively. The 90% CIs for the log-transformed ratios of test tablet to reference tablet for Cmax' AUC0-48' and AUCo~ were 103.9 to 124.9, 94.0 to 111.5, and 94.4 to 111. 7, respectively (all, *P* = NS).The corresponding 90% CIs for the log-transformed ratios of test capsule to reference tablet were 90.8 to 109.2,84.9 to 107.9, and 85.1 to 100.7 (all, P = NS). Ten adverse events were reported during the study;7 subjects complained of pain during blood sampling, and 3 had a blocked venous catheter. No treatment-related adverse events were reported or observed. In this single-dose crossover study in healthy Chinese male volunteers, the test and reference formulations of olmesartanmedoxomil20-mg capsules and tablets met the regulatory criteria for assuming bioequivalence [17]

Steven G. Chrysanth al**,** have done an Evaluation of Antihypertensive Therapy with the Combination of OlmesartanMedoxomil and Hydrochlorothiazide. Olmesartanmedoxomil plus HCTZ produced greater reductions in both SeDBP and seated systolic blood pressure (SeSBP) at week 8 than did monotherapy with either component. All olmesartanmedoxomil/HCTZ combinations significantly reduced SeDBP and SeSBPcompared with placebo in a dose-dependent manner. Reductions from baseline in mean trough SeSBP/SeDBP were 3.3/8.2 mm Hg, 20.1/16.4 mm Hg, and 26.8/21.9 mm Hg with placebo, olmesartanmedoxomil/HCTZ 20/12.5mg, and olmesartanmedoxomil/HCTZ 40/25 mg, respectively. All treatments were well tolerated. Olmesartanmedoxomil/HCTZ combination therapy produced BP reductions of up to 26.8/ 21.9 mm Hg and was well tolerated. [18]

Giuseppe DeRosa et al, examined results from 12 months, randomized, clinical trial comparing an olmesartan/amlodipine single pill combination to olmesartan and amlodipine monotherapies on blood pressure and inflammation 26–

33Olmesartan/amlodipine combination was more effective than amlodipine or olmesartan in reducing blood pressure. Olmesartan/amlodipine combination, but not amlodipine, decreased FPG after 12 months. Olmesartan/amlodipine combination better decreased FPI and HOMA index and increased M value compared to olmesartan and amlodipine monotherapies. Olmesartan/amlodipine significantly decreased chemerin and omentin compared to olmesartan and amlodipine. Other than to be more effective in reducing blood pressure, olmesartan/amlodipine single pill combination gave also a major increase in insulin sensitivity and a decrease of inflammatory markers compared to single monotherapies. [19]

S. Sayed et al, prepared Olmesartanmedoxomil surface solid dispersion-based oro dispersible tablets: formulation and *in vitro* characterization. This work aims to improve the dissolution of the poorly water soluble drug olmesartanmedoxomil by using the surface solid dispersion (SSD) technique. Insoluble carriers, namely Avicel PH 102, Aerosil 200, silicified microcrystalline cellulose, Lycatab, Starlac, sodium starch glycolate (SSG), and Kyron T-314, were used at three different drug: carrier ratios (1:1, 1:5, and 1:9 w/w) to prepare SSDs by solvent evaporation method. SSD18 consisting of drug: SSG at 1:9 ratio and SSD20 consisting of drug: Kyron T-314 at 1:5 ratio showed the highest enhancement in the dissolution rate and efficiency compared to the plain drug and the physical mixture. The selected dispersion was formulated into orodispersible tablets (ODTs) by using four different disintegrants. F3 DC ODT (consisting of SSD20 and 5 % crospovidone) and F6 DC ODT (consisting of SSD18 and no disintegrant) exhibited low in vitro disintegration time and a high percentage of olmesartanmedoxomildissoluted within 10 min. [20]

Steven G. Chrysant, et al**,** evaluated the Efficacy and safety of triple-combination therapy with olmesartan, amlodipine, and hydrochlorothiazide in study participants with hypertension and diabetes: a subpopulation analysis of the TRINITY study. The prespecified changes in BP from baseline for the diabetes subgroup receiving triple-combination treatment were greater than the respective dual-combination treatments (P _ .0013). Also, more participants with diabetes receiving triple combination treatment reached BP goal (<130/80 mm Hg) versus those receiving dual combination treatments. [21]

Henry A. Punziet et al, evaluated Efficacy and safety of olmesartan/amlodipine/HCTZ in hypertensives, not at goal with mono, dual or triple drug therapy: results of the champion study. They assessed the efficacy and safety of once daily olmesartanmedoxomil/ amlodipine besylate/HCTZ 40/10/25mg in patients with hypertension, not at goal with mono, dual or triple drug therapy in phase 4, single-center, prospective, open-label, blinded-endpoint study. Adults with stage 1 or 2 hypertension entered a 2-9 day screening period, followed by a 4-6week open-label treatment with OM/AM/HCTZ fixed dose combination. Safety and tolerability were assessed by recording treatment-emergent adverse events (TEAEs), monitoring vital signs and clinical laboratory parameters, and performing ECGs and physical examinations. Efficacy assessments included a change from baseline in trough sDBP and sSBP and percentage of patients who achieved BP goal. A total of 13 out of 40 patients were _60 years of age (64% men and 36% women). TEAEs were experienced by 86% of patients and were mostly mild or moderate. The most common TEAEs were sinusitis (7.5%), swelling of both ankles (5.0%), tiredness (5.0%) swelling of both lower legs (2.5%) and worsening swelling of both feet (2.5%). There were no dizziness, syncope or serious AEs experienced and no deaths occurred. Mean baseline office SBP/DBP of patients aged _60 years was 140/86 mmHg and mean baseline ABPM SBP/DBP of patients aged _60 years was 134/ 75mmHg. After 24 hours of treatment with triple drug therapy mean office SBP/DBP was 129/79 mmHg (a SBP reduction of 11.2mmHg and a DBP reduction of 7.8mmHg) and mean ABPM SBP/DBP of patients aged _60years was 129/73mmHg (an ambulatory SBP reduction of 5.1mmHg and an ambulatory DBP reduction of 2.3mmHg), after 1 week of treatment, mean office SBP/DBP was 122/77 mmHg (a SBP reduction of 18.2mmHg and a DBP reduction of 9.4mmHg) and mean ABPM SBP/DBP of patients aged _60 years was 120/69mmHg (an ambulatory SBP reduction of 13.6mmHg and an ambulatory DBP reduction of 6.0mmHg), after 2 weeks of treatment, mean office SBP/DBP was 121/ 76 mmHg (an SBP reduction of 18.7mmHg and a DBP reduction of10.2mmHg) and mean ABPM SBP/DBP of patients aged _60 years was 118/67mmHg (an ambulatory SBP reduction of 15.3mmHg and an ambulatory DBP reduction of 7.8mmHg), and after 4 weeks of

treatment, mean office SBP/DBP was 119/76 mmHg (an SBP reduction of 21.6mmHg and a DBP reduction of 10.7mmHg) and mean ABPM SBP/DBP of patients aged _60 years was 116/67mmHg (an ambulatory SBP reduction of 17.2mmHg and an ambulatory DBP reduction of 8.2mmHg). In conclusion, triple drug therapy resulted in lower achieved SBP reduction (<140 mmHg) in patients over 60 and was well tolerated and without adverse effects on health or quality of life. As per JNC 8 recommendations, the triple drug treatment would not need to be adjusted in these patients. [22]

Elizabeth O. Ofili, et al, studied the difference between the Moderate versus intensive treatment of hypertension using amlodipine/valsartan and with the addition of hydrochlorothiazide for patients uncontrolled on angiotensin receptor blocker monotherapy: results in racial/ethnic subgroups. Combination therapy may reduce racial/ethnic differences in response to antihypertensives. In this posthoc analysis, we evaluated treatment response by race/ethnicity among hypertensive adults enrolled in a 12-week, double-blind study in which patients previously uncontrolled (mean sitting systolic blood pressure [MSSBP] _150 and <200 mm Hg) on angiotensin receptor blocker (ARB) monotherapy (other than valsartan) for 28 days or more (n ¼ 728) were randomized to amlodipine/valsartan 10/320 mg (intensive) or 5/160 mg (moderate). Treatment-na€ıve patients (in previous 28 days) or those who failed on a non-ARB first underwent a 28-day run-in period with olmesartan 20 mg or 40 mg, respectively. Hydrochlorothiazide (HCTZ) 12.5 mg was added to both arms at week 4; optional up-titration to 25 mg at week 8 (if MSSBP >140 mm Hg). Intensive treatment provided greater BP lowering versus moderate treatment throughout the study, regardless. [23]

AIM AND OBJECTIVE

AIM AND OBJECTIVE

AIM:

To determine the direct compression of Amlodipine Besylate and Olmesartan Medoxomil using by SeDem.

OBJECTIVES:

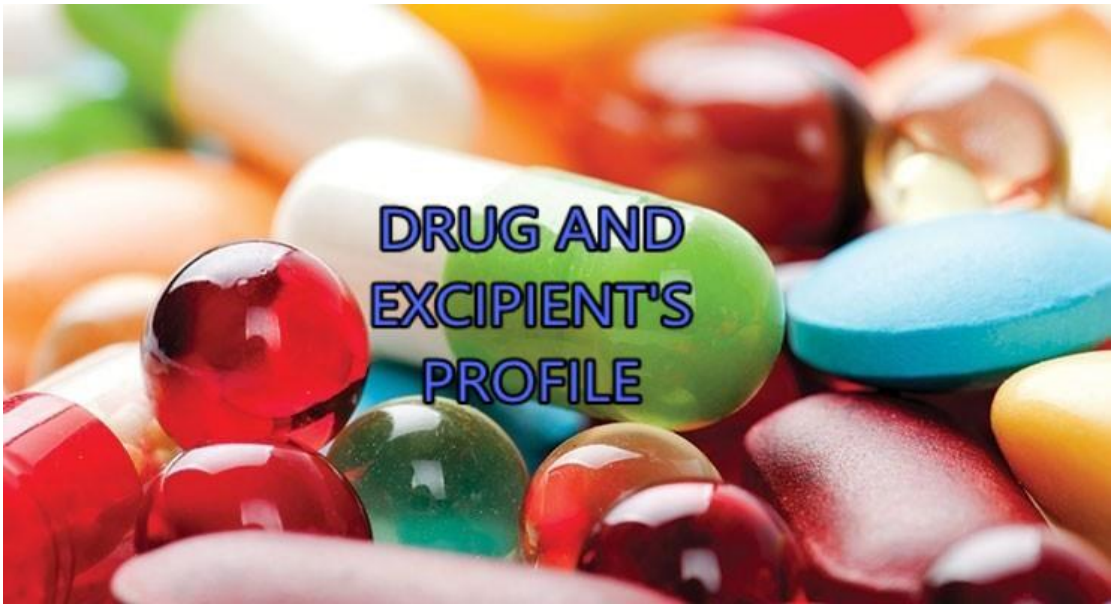
- To developed and formulate the Amlodipine Besylate and Olmesartan Medoxomil tablet in direct compression method using by SeDem
- The high cost of imported custom made directly compressible adjuvant. The primary reason for high cost of imported direct compression diluents is the use of spray drying.
- Price control is One of the objectives of the present investigation was to develop an economical adjuvant so that the domestic manufacturers can meet the requirements of price control. The cost of starch is less as compared to that of lactose or MCC. Hence, starch based directly compressible adjutants were developed in the present investigation
- Blends of treated starch also are explored for preparing quickly disintegrating tablets. A systematic evaluation of various blends of physically modified starch and microcrystalline cellulose or lactose for direct compression


WORK
the
PLAN

PLAN OF WORK

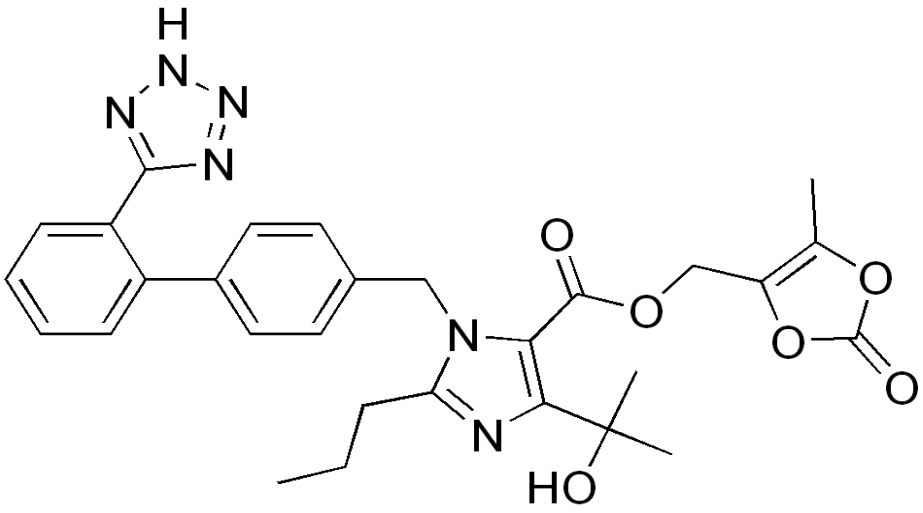
The study was planned to carry out as follow,

- Collection of literature review
- Olmesartan medoxomil and Amlodipine besylate drug collection
- Effect on solubility
- Calibration curve of Olmesartan medoxomil and Amlodipine besylate
- SeDem parameters
    - Bulk density
    - Tapped density
    - Inter-particle porosity
    - Carr index
    - Cohesion index
    - Hausner ratio
    - Angle of repose
    - Flow ability
    - Loss on drying
    - Hygroscopicity
    - Particle size
    - Homogeneity index
- Direct compression of the tablets
- Evaluation study of tablets
    - Weight variation test
    - Friability test
    - Hardness test
    - Dissolution test
- SEM analysis of formulated tablets


DRUG AND
EXCIPIENT'S
PROFILE

DRUG PROFILE

OLMESARTAN MEDOXOMIL:



(5-methyl-2-oxo-1, 3-dioxol-4-yl) methyl-5-(2-hydroxypropan-2-yl)-2-propyl-3-[[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] imidazole-4-carboxylate

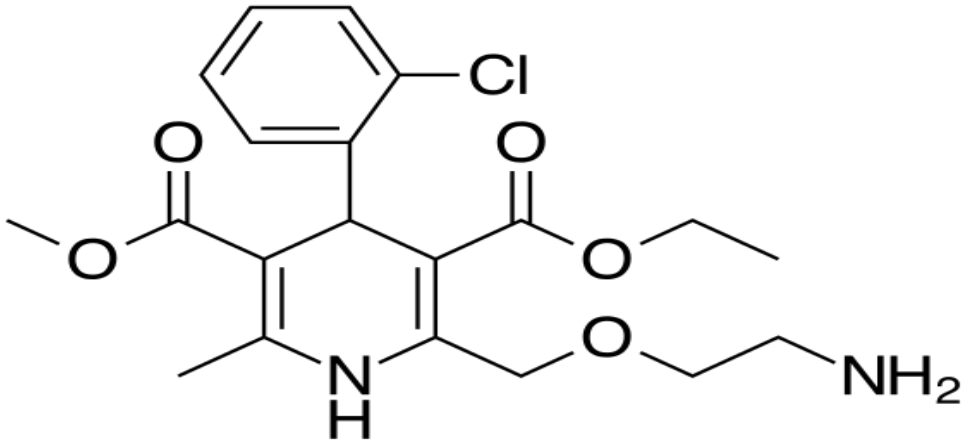
Mechanism of Action

Angiotensin II is created from angiotensin I in a response catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the major presser cause of the renin-angiotensin system, with the effect that contains vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Two subtypes make up the angiotensin II receptor: AT_1 and AT_2. Olmesartan Medoxomil blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its act is, therefore, independent of the pathway for angiotensin II synthesis.

The Pharmacokinetic and Metabolic Profile of Olmesartan Medoxomil

Orally administer Olmesartan Medoxomil was quickly absorbed from the gastrointestinal tract and changed through absorption to olmesartan, the pharmacologically active metabolite that was consequently excreted with no further metabolism. The medoxomil moiety was released as di acetyl that was rapidly cleared by further metabolism and excretion. Peak plasma concentrations of olmesartan occur 1-3 h following administration, after which concentration decreased quickly. The elimination half-life was 10-15 h. Olmesartan Medoxomil was not assessable in plasma excretion. The quantity of distribution was low, reliable with limited extra vascular tissue distribution. Bioavailability (Cmax and area under the curve) increased around in proportion to dose, later than single and multiple daily oral doses, more the therapeutic dose range (up to 40-80 mg daily), above which systemic availability of Olmesartan Medoxomil increased a lesser amount of the proportionally with the increase in dose. Steady-state plasma concentrations of Olmesartan Medoxomil were reached within the first little daily oral doses. On average, approximately 40% of systemically available olmesartan medoxomil was excreted by the kidneys, the remains life form excreted in feces, following secretion in bile. Renal clearance (0.5-0.7 l/h) was self-determining of dose, accounting for approximately 9-12% of an oral dose. The absolute bioavailability of olmesartan from Olmesartan medoxomil tablets was 28.6%. Olmesartan Medoxomil exhibits little or no required to blood cells. No clinically major steady-state pharmacokinetic interactions were observed following co-administration of Olmesartan Medoxomil with digoxin, warfarin, and aluminum magnesium hydroxide (antacid), supporting the low possible for clinically important pharmacokinetic interactions to occur between Olmesartan Medoxomil and co-administered drugs. [24]

AMLODIPINE BESYLATE



3-**Ethyl**-5-methyl (±)-2-[(2-**aminoethoxy**) methyl]-4-(2- **chlorophenyl**)-1,4-**dihydro**-6-methyl-3,5-**pyridinedicarboxylate**, monobenzenesulphonate.

Mechanism of Action of Amlodipine Besylate:

Amlodipine Besylate is a dihydropyridine calcium competitor (calcium ion competitor or slow-channel blocker) that inhibits the Trans membrane entry of calcium ions into vascular soft muscle and cardiac muscle.

Pharmacokinetics of Amlodipine Besylate:

Amlodipine Besylate is a di-hydro pyridine calcium opponent drug with the typical pharmacokinetic character which appears to be attributable to a far above the ground extent of ionization. Following oral administration, bioavailability is 60 to 65% and plasma concentrations increase step by step to peak 6 to 8h later than administration. Amlodipine Besylate is expansively metabolized in the liver (but there is no significant pre-systemic or first-pass metabolism) and is little by little clear with a deadly elimination half-life of 40 to 50h. The volume of distribution is bulky (21 L/kg) and around is a high degree of protein binding (98%). There is some evidence that age, strict hepatic impairment, and strict renal impairment power the pharmacokinetic profile most important to higher plasma concentration and longer half-lives. There is no proof of pharmacokinetic drug interactions. Amlodipine Besylate shows linear dose-related pharmacokinetic character and, at steady-state,

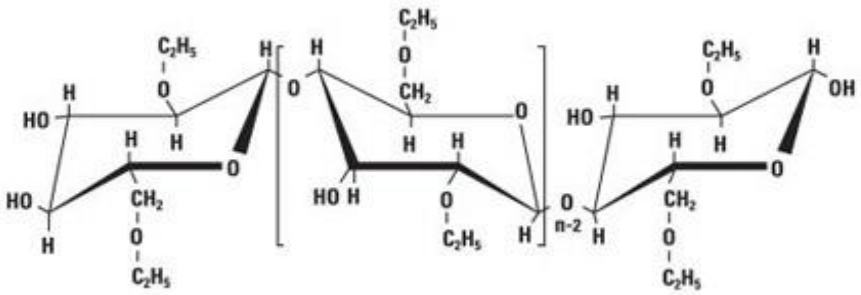
there are relatively small fluctuations in plasma concentration across a dosage interval. Thus, even though structurally connected to previous dihydropyridine derivatives, Amlodipine Besylate displays extensively different pharmacokinetic characteristics and is apposite for administration in a single daily dose. [25]

EXCIPIENTS PROFILE

ETHYL CELLULOSE:

Ethyl cellulose is a derived of cellulose in which a number of-of the hydroxyl group on the repeating glucose units are changed into ethyl ether groups. The number of ethyl groups can differ depending on the manufacturer. It is primarily used as a thin film matter. Ethyl cellulose is used as a food preservative as an emulsifier.

Structure:



Synonyms:

Cellulose, ethyl ether; ethylated cellulose; ethyl cellulose

Chemical Name:

Ethyl cellulose, Aqua coat, Ethel, Surelease

Molecular Formula:

$C_{20}H_{38}O_{11}$

Molecular Weight:

454.513 g/mol

Physical Properties:

1. **Colour:**

   Pale needles since benzene [26], Free-flowing, white to brightness tan powder [27] vacant commercially as an obvious layer or sheet [28], White, granular, thermoplastic solid. [29]

2. **Melting point:**

   240-255˚C [30]

3. **Solubility:**

   Impenetrable in glycerin and propylene glycol (31) Freely soluble in a blend of Pungent hydrocarbons by alcohol [32] have an ethyl degree of alternative (DS) in the range of ~2.2 - 2.7. Water soluble at DS ~1.2.Above a DS of ca 2.5, soluble in a lot of polar solvents. [33]Soluble in mainly pure liquids

4. **Density**

   1.07-1.18[34]

5. **stability:**

   Extremely steady chemically, Cellulose ethers. [35]

6. **pH**

   Aqueous suspensions are neutral to litmus. [36]

Applications:

1. description of Ethyl cellulose Films contain Natural Polysaccharides by Thermal examination and FTIR Spectroscopy
2. estimate of ethyl cellulose as a matrix for controlled release drug delivery
3. Physico-Mechanical examination of Free Ethyl cellulose Films Plasticized with Incremental mass Percents of DibutylSebacate

4. appliance of an Aqueous Ethyl cellulose distribution in Multiple-Unit Pellet system
5. exercise of Xanthan Gum and Ethyl cellulose in Formulation of Metronidazole for Colon release
6. appliance of Ethyl cellulose in Preparation of extensive Release Theophylline Inert Matrix Tablets by Wet Granulation
7. Starch or amylum is a polymeric carbohydrate consisting of a big number of glucose units connected by glycoside bond. This polysaccharide is formed by most green plants as an energy store up. It is the mainly common carbohydrate in human diets an

STARCH

It is restricted in great amounts in staple foods such as potatoes, wheat, maize (corn), rice, and cassava. Pure starch is a white, tasteless and odorless powder that is insoluble in freezing water or alcohol. It consists of two type of molecules: the linear and helical amylose and the branched amylopectin. Depending on the plant, starch generally contains 20 to 25% amylose and 75 to 80% amylopectin by weight.[37] Glycogen, the glucose store up of animals, is a more divided version of amylopectin.

Molecularformula:

$(C_6H_{10}O_5)\ n$

Appearance:

White powder

Density:

1.5g/cm^3

Melting point:

Decomposes

Solubility:

Solubility in Water: insoluble (see starch gelatinization)

Applications:

1. Paper making is the major nonfood appliance for starches globally, consuming millions of metric tons annually

2. Ribbed penetrate adhesives are the next major application of non-food starches internationally. Starch glue is mainly based on unchanged native starches, plus some preservative such as borax and caustic soda.

3. Clothes or laundry starch is a fluid to arranged by mixing a vegetable starch in water and is used in the launder of clothes

4. Textile chemical from starch: bend sizing agents are used to reduce breaking of yarn in weaving.

5. Starch is primarily used to size cotton base yarn. Modified starch is as well used as a textile print thickener.

6. During oil assessment, starch is use to accurate the viscosity of drill fluid, which is use to lubricate the drill top and suspend the mill remains in petroleum origin.

7. Starch is also used to create some packing peanuts and a number of drop ceiling tiles.

8. In the printing manufacturing, food quality starch [38] is use in the produce of ant setoff spray powder used to separate printed sheets of paper to avoid wet ink organism set off.

9 .For body powder, powdered corn starch is used as an alternative for talcum powder, and equally in previous health and beauty products.

10. Starch is used to generate a range of bioplastics, artificial polymers that are biodegradable. An example is a polylactic acid base on glucose from starch.

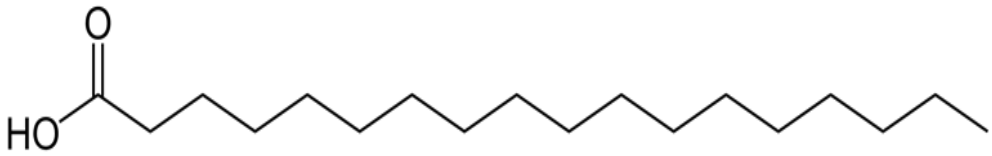
11. Glucose from starch can exist further fermented to biofuel corn ethanol using the so-called wet milling process. Today most bioethanol manufacture plants use the dry mill process to agitation corn or other feedstock straight to ethanol. [39]

12. Hydrogen manufacture can use glucose from starch as the raw material, using enzymes.

STEARIC ACID

It a saturated fatty acid with an 18carbon sequence and has the IUPAC name octadecanoic acid. It is a waxy solid and its substance formula is $C_{17}H_{35}CO_2H$. Its name comes from the Greek word "*stear*", which means tallow. The salts and esters of stearic acid are called stearates. As its ester stearic acid is on own of the primarily universal saturated fatty acids found in nature follow palmitic acid.[40] The triglyceride derived from three molecules of stearic acid is call stearin.

Structure:



Chemical formula:

$C_{18}H_{36}O_2$

Molar mass:

284.48 g·mol−1

Appearance:

White solid

Odour:

Pungent, oily

Density:

0.9408g/cm^3 (20 °C)

0.84 g/cm^3 (70 °C)

Melting point:

69.3 °C (156.7 °F; 342.4 K)

Boiling point

361 °C (682 °F; 634 K)

Decomposes

232 °C (450 °F; 505 K)at 15 mmHg[41]

Solubility

Soluble in alkyl acetates, alcohols, $HCOOCH_3$, phenyls, CS_2, CCl_4[42]

Application:

1.In universal, the application of stearic acid develops its bifunctional nature with a polar top group that can be attached to metal cations and a no polar chain that confer solubility in organic solvents.

2. The grouping leads to uses as a surfactant and softening agent. Stearic acid undergo the typical reaction of saturated carboxylic acids, a noteworthy

One being a reduction to stearyl alcohol, and etherification with a range of alcohols.

3. This is used in a large variety of manufacture, from simple to difficult electronic devices.

Magnesium stearate:

Magnesium stearate is the substance with the formula Mg(C18H35O2)2. It is soap, consisting of salt contain two equivalent of stearate (the anion of stearic acid) and one magnesium cation (Mg2+). Magnesium stearate is a white, water-insoluble powder. Its applications exploit its softness, insolubility in many solvents, and low toxicity. It is used as a release mediator and as a component or lubricant in the manufacture of pharmaceuticals and cosmetics. [50]

IUPAC name:

Magnesium octadecanoic

Chemical formula:

Mg (C18H35O2)2

Molar mass:

591.27 g/mol

Physical Properties:

Appearance:

Light white powder

Odour:

Slight

Density:

1.026g/cm^3

Melting point:

88.5 °C (191.3 °F; 361.6 K)

Solubility in water:

0.003 g/100 ml (15 °C)

0.004 g/100 ml (25 °C)

0.008 g/100 ml(50 °C)

Solubility:

Negligible in ether and alcohol

Slightly soluble in benzene

Applications:

1. Magnesium stearate is frequently used as an anti-adherent [51] in the generate of medical tablets, capsules, and powders.[43]
2. Magnesium stearate can moreover be used effectively in dry coating processes[44,45,46]
3. Magnesium stearate is also used to attach sugar in hard candies like mints and is a general element in baby formulas.

MATERIALS AND MANUFACTURER

MATERIALS AND MANUFACTURER

S.NO	NAME OF THE MATERIAL	SOURCE/SUPPLIER/MANUFACTURER
1.	SODIUM HYDROXIDE	MOLYCHEM
2.	POTASSIUM DIHYDROGEN ORTHO PHOSPHATE	REACHEM LABORATORY
3.	AMLODIPINE BESYLATE	GIFT SAMPLE OF CAREWELL, CHENNAI.
4.	OLMESARTAN MEDOXAMIL	GIFT SAMPLE OF G.K.M. LABORATORY, PUTHUCHERRI.
5.	STARCH	FISCHER LABORATORY REAGENT
6.	ETHYL CELLULOSE	ROLEX LABORATORY
7.	STEARIC ACID	HIMEDIA LABORATORIES.Pvt.Ltd
8.	MAGNESIUM STEARATE	MODERN SCIENTIFIC.CO
9.	ETHYL CELLULOSE LR	SDFINE – CHEM. Ltd

LIST OF EQUIPMENTS / INSTRUMENT'S

LIST OF EQUIPMENTS/ INSTRUMENTS

S.NO	EQUIPMENTS/ INSTRUMENTS	MANUFACTURE/SOURCE
1.	ELECTRONIC BALANCE	SHIMADZU ELB 300
2.	HOT AIR OVEN	ELCON
3.	MAGNETIC STIRRER	REMI
4.	DISSOLUTION TEST APPARATUS	LABINDIA DISSOO 2000
5.	UV SPECTRO PHOTO METER	SHIMADZU UV -1700
6.	PH	AGRONIL 511
7.	MICROSCOPE	A.K.C.P
8.	TABLET COMPRESSION MACHINE	RIMEK MINI PRESS-1
9.	DISINTEGRATION TEST APPARATUS	ROLEX
10.	SEM ANALYSER	ZEISS-5200 SEM

EXPERIMENTAL WORK

EXPERIMENTAL WORK

DEVELOPMENT OF CALIBRATION CURVE:

Preparation of Buffer Solution (pH-7.4) [47]

750ml of potassium dihydrogen phosphate solution (27.218gm of potassium dihyrogen ortho phosphate in 1000ml) and 586.5ml of NaoH (8gm in 1000ml) were mixed properly and the volume was made up to 1000ml with distilled water

Preparation of Standard Solution of Amlodipine Besylate Sample: [48]

A solution of 10mg Amlodipine Besylate was prepared by dissolving in 5ml ethanol and 95ml phosphate buffer pH 7.4, from which 0.5ml was withdrawn in separate volumetric flask and dilute to make 10ml with phosphate buffer to produce 5µg/ml concentration and absorbance at 365nm.

Preparation of Working Solution:

From standard solution 0.5, 1, 1.5, 2 and 2.5 was withdrawn in five 10ml volumetric flask and dilute to make 10ml with phosphate buffer pH 7.4, to produce concentration 5, 10, 15, 20 and 25µg/ml respectively. The solution were analysed by UV-Spectrophotometer at 365nm and result were recorded. The calibration graph was plotted as concentration on x-axis vs. absorbance on y-axis.

Table No: 7.1 Standard Curve of Amlodipine Besylate:

S.No.	Concentration (µg/ml)	Absorbance	Slope	Average Slope
1.	5	0.051	0.0102	0.011752
2.	10	0.116	0.0116	
3.	15	0.179	0.0119	
4.	20	0.242	0.0121	
5.	25	0.324	0.01296	

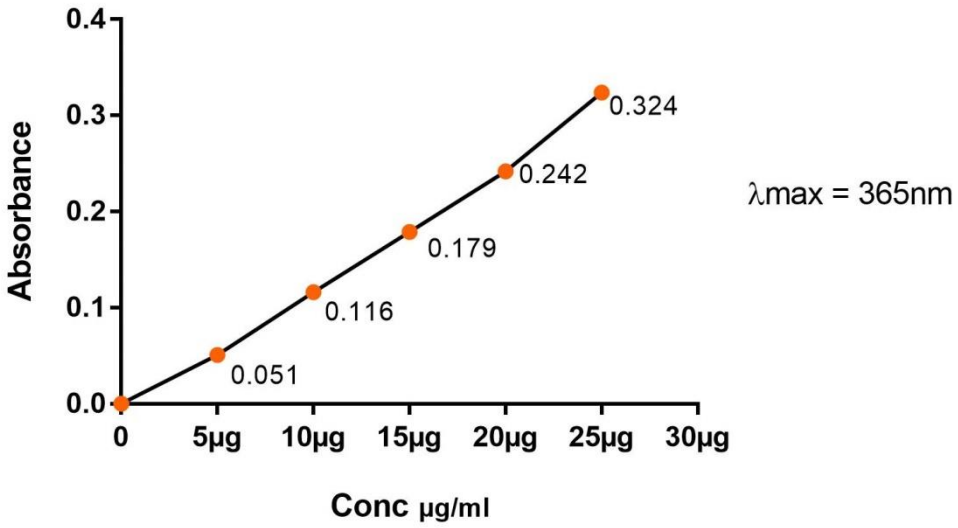


Figure: 7.1 Standard Curve of Amlodipine Besylate

Preparation of Standard Solution of Olmesartan Medoxomil Sample: [48]

A solution of 10mg Olmesartan Medoxomil was prepared by dissolving in 5ml ethanol and 95ml phosphate buffer pH 7.4, from which 0.5ml was withdrawn in separate volumetric flask and dilute to make 10ml with phosphate buffer to produce 5µg/ml concentration and absorbance at 257nm

Preparation of Working Solution:

From standard solution 0.5, 1, 1.5, 2 and 2.5 was withdrawn in five 10ml volumetric flasks and dilute to make 10ml with phosphate buffer pH 7.4, to produce concentration 5, 10, 15, 20 and 25µg/ml respectively. The solution was analyzed by UV-Spectrophotometer at 257nm and result were recorded. The calibration graph was plotted as concentration on x-axis vs. absorbance on y-axis

Table No: 7.2Standard Curve of Olmesartan Medoxomil:

S.No.	Concentration (µg/ml)	Absorbance	Slope	Average Slope
1.	5	0.169	0.0338	0.035914
2.	10	0.387	0.0387	
3.	15	0.481	0.0320	
4.	20	0.771	0.03855	
5.	25	0.913	0.03652	

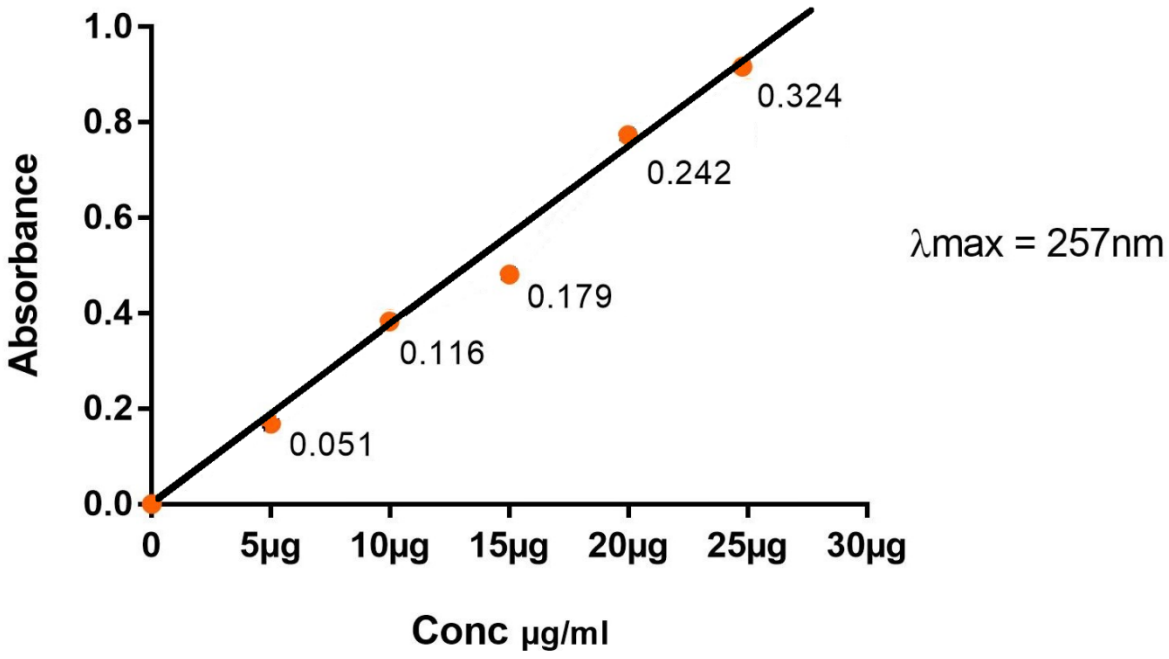


Figure: 7.2 Standard Curve Of Olmesartan Medoxomil

Effect on Amlodipine Besylate Solubility:

A known amount of sample of Amlodipine Besylate added in 50ml of ethanol and kept for 3 hours occasionally stirring. After 3 hours contents were filtered through the Whatman filter paper and appropriate dilutions were made with 0.2M phosphates buffer and the absorbance of the resultant solution was measured at 365nm and extrapolated on the standard graph to determine the concentration.

Effect on Olmesartan Medoxomil Solubility:

A known amount of sample of Olmesartan Medoxomil added in 50ml of ethanol and kept for 3 hours occasionally stirring. After 3 hours contents were filtered through the Whatman filter paper and appropriate dilutions were made with 0.2M phosphate buffer and the absorbance of the resultant solution was measured at 257nm and extrapolated on the standard graph to determine the concentration.

SEDEM PARAMETERS:

Bulk Density (Da): [49]

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the trend of the particles to remain to one another.

Method:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A measure of correctly weigh powder (bulk) since each formula,

Before shaken to crack any agglomerates formed was introduced into a 100ml measuring cylinder. Behind the primary volume was observed, the cylinder be allowed to reduce under its own weight on to a hard surface from the height of 2.5cm at 2 sec interval. The tapping is constant until no additional change in volume was noted.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of the powder}}{\text{Bulk volume}}$$

Tapped Density (Dc):[50]

The measuring cylinder contain a known mass of blend was tapped for an unchanging time. The smallest amount volume (Vt) full in the cylinder and the weight (M) Of the blend was measured. The tapped density (**λ**t) be calculate using the track formula

$$t = \frac{M}{V}$$

Where,

M = Mass of the powder

V = Tapped volume

t = Tapped density

Carr Index (Ic):

This is calculated from Da and Dc as

$$Ic = \frac{(Dc - Da)}{Dc} \times 100$$

Cohesion Index (Icd):

The maximum value is determined empirically from compression test on many powdered substances, based on the largely hardness obtained with no producing capped or broken tablets. This stiffness is then establish as the maximum limit. The minimum value is “0”. These values imply that no tablets are obtained when the powders are compressed. The denote stiffness (N) of the tablets is calculated. First, the untreated powder is tested, however if it cannot be compressed, 3.5% of the following combination is added to the mix: talc¼2.36%, Aerosil (Evonik, Germany) 200¼0.14% and magnesium stearate¼1.00%.

Hausner’s ratio (IH): [51]

Hausner’s ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$IH = \frac{Dc}{Da}$$

Angle of Repose (θ): [52]

The frictional forces during a loose powder or granules can be measured by the angle of repose. This is the most direction possible between the plane of a pile of powder or granules and the horizontal plane.

$$\tan\theta = h/r \quad \theta = \tan^{-1}(h/r)$$

Where θ is the angle of repose, h is the height, r is the radius.

Table No: 7.2 a Angle Of Repose Flow Property

S.No	Angle Of Repose	Flow Property
1.	Less than 25˚	Excellent flow
2.	25˚ to 30˚	Good
3.	30˚ to 40˚	Possible flow
4.	greater than 40˚	Very poor

Funnel Method:

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph, the sheet was taken to measure the area of the pile, there by evaluating the flow ability of the granules. The height of the pile was also measured.

Open End Cylinder Method:

10g of powder was weighed accurately with an electronic weighing balance. The powder was then put into a cylinder that was stopped by rubber closure at one end. The cylinder was pulled and the mixtures were allowed to flow down to form a heap on the stopper. The height, diameter and angle height of the powder heap were recorded. The angle of repose of the powder mass was calculated.

Flowability (t″): [53]

It is expressed in seconds and tenths of a second per 10 grams of sample, with a mean value of two measurements

1) Open end cylinder method
2) Funnel method

LOSS ON DRYING (%HR)

PROCEDURE

Dry a weighing bottle for about 30 minutes under the prescribed conditions, allow cooling it in desiccators if heated, and weigh it accurately. If the powder is large crystals or lumps, promptly crush it into particles not larger than about 2 mm in diameter and, unless otherwise specified, place 1 to 2 g into the weighing bottle, spread the powder so that the layer is not thicker than 5 mm, and weigh it accurately. Place the bottle in the drying oven, remove the stopper (placing it nearby), dry under the specified conditions, stopper again, take the bottle out of the oven, and weigh it again. If heated, unless otherwise specified, allow to cool it in desiccators, and weigh it accurately. If the powder melts at a temperature lower than the specified drying temperature, dry it at a temperature 105 °C ± 2 °C lower than the melting temperature for 1 to 2 hours, and dry it under the specified conditions.

Loss on drying = Initial weight of the drug – Final weight of the drug X 100

HYGROSCOPICITY (%H):

Determination of the percentage increase in sample weight after being kept in a humidifier at a relative humidity of 76% (±2%) and a temperature of 22°C± 2°C for 24 h.

Hygroscopicity = (Final weight of the drug – initial weight of the drug) X 100

PARTICLE SIZE (% PF) OF DRUG BY EYE PIECE MICROMETER:

PRINCIPLE:

The particle size can define as the diameter of the sphere, equivalent to the particle in weight, volume, surface area, and projected area. When the particle size is analyzed by microscope, it is referred as the projected diameter of the sphere, which is the same projected area of the particle size with the effective procedure. It is the only method in which direct measurement of the particles is made. The particle size distribution is represented in the graphical form as “Histogram” – Frequently distribution curve or cumulative distribution curve. Some samples may be similar

average size but differ in distribution. Such differences are flatted in a graphical form as “Histogram”. It gives the number of the particle diameter but not actual size. The cumulative distribution curve gives the % of any given sample.

PROCEDURE:

Calibration of the Eyepiece micrometer is done with the division of Eyepiece micrometer scale co-inside with the division of the stage micrometer.

CALIBRATION OF EYEPIECE MICROMETER:-

1 Division of stage micrometer = 0.01mm = 10 micron

$$1 \text{ Division of Eye-piece micrometer} = \frac{\text{No. of division of stage micrometer}}{\text{No. of division of Eyepiece Micrometer}} \times 10\mu$$

A small amount of the sample is diluted with the solvent (water, liquid paraffin (or) Glycerine) few drops of the above solution is transferred on a glass side and focused under a microscope by using an Eyepiece micrometer, the diameter of the 100 particles determined by the number of the division of Eye-piece micrometer. This is then converted to microns the particles are arranged on the basis of the size range; the number of the particles in each size range are then counted and calculated. Then the percentage in each interval and percentage undersize are calculated. The histogram and cumulative curves are flatter.

DETERMINATION OF SAMPLE DRUG PARTICLE SIZE BY SIEVING METHOD

PRINCIPLE:

Particle size can affect the flow property method of sieving may be employed for screening material fine as under 100μ. The Sample powder is shaken for a definite period of time and material passes through the one sieve retained on the next fine sieve, collect and weigh the sample. The sieves are arranged in a nest with the coarse at the top and fine at the bottom. Carefully weigh the sample of the

powder, placed on the top sieve and after the sieves are shaken for free determine period of time, the sample powder retain on each sieve is weighed. An arithmetic mean of the sample is determined.

PROCEDURE:

10gm of the sample is weighed and placed on the top sieve of the arranged sieves, mechanically shaken for 20 minutes. The sieves are then removed and the drug was retained on each sieve are weighed and the results are calculated. The percentage weight of the powder retain is calculated. Weight size is calculated from the percentage weight of the retained. Arithmetic mean is calculated. The percentage undersize is calculated by adding the value of the percentage of the weight of powder. The percentage oversize is calculated by the values, the percentage of the weight of drug retained. Cumulative percentage curves are plotted.

Weigh size = Arithmetic mean size of opening x percentage of powder obtained

$$\text{Arithmetic mean} = \frac{\text{Weigh size}}{100}$$

Percentage under size (adding up to weight size) Percentage oversize (From the 100 subtract the values)

HOMOGENEITY INDEX (Iθ):

To determine particle size by means of the sieve test, the grain size of a 100g sample is measured by subjecting a sieve stack to vibration for 10 min at speed 10 (CISA vibrator). The sieve sizes used are 0.355 mm, 0.212 mm, 0.100 mm and 0.05 mm. The percentage of product retained on each sieve is calculated and the amount that passes through the 0.05mm sieve is measured. The percentage of fine particles (<50 μm) (%Pf) was calculated as described above. Note that if this percentage is higher than that calculated in the complete sieve test, it is because some of the particles become Expert Systems for Human, Materials and Automation 20 adhered to the product retained in the sieves during the grain-size test, and the percentage of <50 μm particles found may be lower than the true figure. The following equation is then applied to the data obtained.

$$I\theta = \frac{Fm}{100+(dm-dm-1)Fm-1+(dm+1-dm)Fm+1+(dm-dm-2)Fm-2+(dm+2-dm)Fm+2 +(dm-dm-n)Fm-n+(dm+n-dm)Fm+n}$$

Where:

- Iθ, Relative homogeneity index. Particle size homogeneity in the range of the fractions studied;
- Fm, percentage of particles in the majority range;
- Fm−1, percentage of particles in the range immediately below the majority range;
- Fm+1, percentage of particles in the range immediately above the majority range;
- n, order number of the fraction studied under a series, with respect to the major fraction;
- dm, mean diameter of the particles in the major fraction;
- dm−1, mean diameter of the particles in the fraction of the range immediately below the majority range;
- dm+1, mean diameter of the particles in the fraction of the range immediately above the majority range.

Tablet Compression:

Direct compression is the simplest and most economical method to manufacture tablets with active pharmaceutical ingredients(API) being blended with other directly compressible ingredients.

Table No: 7.3 Amlodipine Besylate Formulation Formula:

S.No	Ingredients	Official Formula For 1 Tablets(mg)	Working Formula For 50 Tablets(g)
1.	Amlodipine Besylate	10mg	0.5mg
2.	Starch	69.62mg	3.481g
3.	Ethyl cellulose	69.62mg	3.481g
4.	Magnesium stearate	0.74mg	0.037g
5.	Total	**150mg**	**7.499g**

Table No:7.4 Olmesartan Medoxomil Formulation Formula:

S.No	Ingredients	Official Formula For 1 Tablets(mg)	Working Formula For 50 Tablets(g)
1.	Olmesartan Medoxomil	10mg	0.5g
2.	Starch	69.62mg	3.481g
3.	Ethyl cellulose	69.62mg	3.481g
4.	Stearic acid	0.74mg	0.037g
5.	Total	**150mg**	**7.499g**

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following parameters.

A. Weight Variation:

20 tablets were weighed both collectively and individually. From the collective weight, the average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether they are within permissible limits or not.

$$\% \text{ Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

B. Hardness:

The hardness of tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

C. Friability:

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre-weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability was calculated using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

D. *In-Vitro* dissolution studies:

Dissolution rate was studied using USP II paddle dissolution apparatus, in 900ml of phosphate buffer at 37±0.5˚ at 100 rpm. Aliquot of dissolution medium was withdrawn at regular time intervals and the same volume of pre-warmed (37±0.5˚) fresh dissolution medium was replaced. The samples were filtered and drug content of Olmesartan Medoxomil and Amlodipine Besylate in each sample was analyzed after suitable dilution by Shimadzu UV-Spectrophotometer at 257 nm & 365 nm individually.

E.SEM [Scanning Electron Microscope]

SEM analysis used to measure the particle size and shape. The morphological appearance of the electrospun fiber and that fiber were investigated by a ZEISS-5200 scanning electron microscope (SEM), operating at an acceleration voltage of 20 KV. For each sample, the average diameter of the individual fibers was measured from multiple SEM images at the magnification of 2.0 KX by semaphore 4.0 software. The result of each sample was reported as an average value from at least three measurements. A Lloyd LRX universal tester was used to determine the mechanical integrity of some of the as-spun fibers. The gauge length and the crosshead speed were 10 µm per minute, respectively. [54, 55]


Result

RESULT AND DISCUSSION

AMLODIPINE BESYLATE:

Bulk Density (Da):

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of the powder}}{\text{Bulk volume}}$$

$$= \frac{10}{32}$$

$$= \mathbf{0.31\ gm/ml}$$

The acceptable range of Bulk density is 0 - 1g/ml in my study Amlodipine Besylate bulk density range is 0.31 gm/ml so this drug is allow suitable for direct compression by SeDeM

Tapped density (Dc):

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume}}$$

$$= \frac{10}{22}$$

$$= \mathbf{0.45\ gm/ml}$$

The acceptable range of Tapped density is 0 – 1g/ml in my study Amlodipine Besylate Tapped density range is 0.45gm/ml so this drug is make suitable for direct compression by SeDeM

Average bulk density:

$$\text{Average bulk density} = \frac{Da + Dc}{2}$$

$$= \frac{0.31 + 0.45}{2}$$

= **0.38 gm/ml**

Inter Particle Porosity (Ie):

$$\text{Inter particle Porosity} = 1 - \left[\frac{Da}{Dc}\right]$$

= 1 – (0.31/0.45)

Porosity = 1- 0.688

= **0.311**

The acceptable range of Inter Particle Porosity is 0 – 1.2 Amlodipine Besylate Inter Particle Porosity range is 0.311 so this drug is suitable for direct compression by SeDeM

Carr's Index (Ic):

$$Ic = \frac{(Dc - Da)}{Dc} \times 100$$

$$= \frac{0.45 - 0.31}{0.45} \times 100$$

= 0.311 x 100

= **31.11%**

The acceptable range of Carr Index is 0 – 50 % in my study Amlodipine Besylate Carr's Index range is 31.11%so this drug is agreed to suitable for direct compression by SeDeM.

Cohesion Index (Icd):

The acceptable range of Cohesion Index is 0 – 200N but our Amlodipine Besylate Cohesion Index is 1.22N so this drug is making suitable for direct compression by SeDeM.

Hausner's ratio (IH):

$$IH = \frac{Dc}{Da}$$

$$= \frac{0.45}{0.31}$$

= **1.451**

When it is the tapped density and d is bulk density. Lower H(<1.25) indicates better flow properties than higher ones(>1.25). The acceptable range of Hausner's ratio is 1 – 3 Amlodipine Besylate Hausner's ratio is 1.451 so this drug is suitable for direct compression by SeDeM.

Angle of Repose (θ):

$$\tan\theta = h/r \quad \theta = \tan^{-1}(h/r)$$

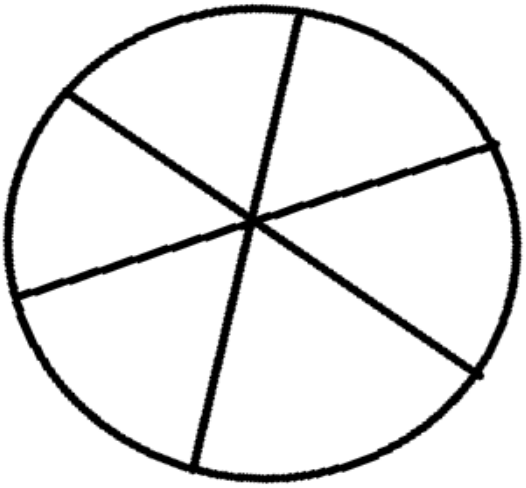
Table No: 8.1Angle of Repose of Amlodipine Besylate by Funnel Method

Name of the Drug Powder	**Height of the Pile (h) cm**	**Diameter of the Pile (d) cm**	**Radius of the Pile (r) cm**	**h/r**	**Q= $\tan^{-1}$ (h/r)**	**Average**
Amlodipine besylate	2.4	7.3	3.7	0.65	33˚.02’	
	2.5	7.3	3.7	0.68	34˚.21’	33˚.02’
	2.2	7	3.5	0.63	32˚.21’	

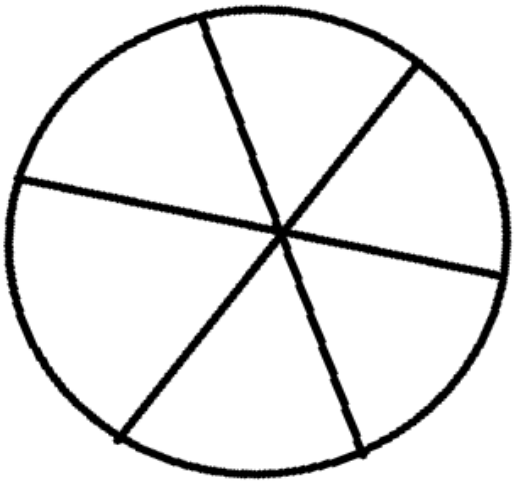
ANGLE OF REPOSE OF AMLODIPINE BESYLATE DRUG BY FUNNEL METHOD

GRAPH:

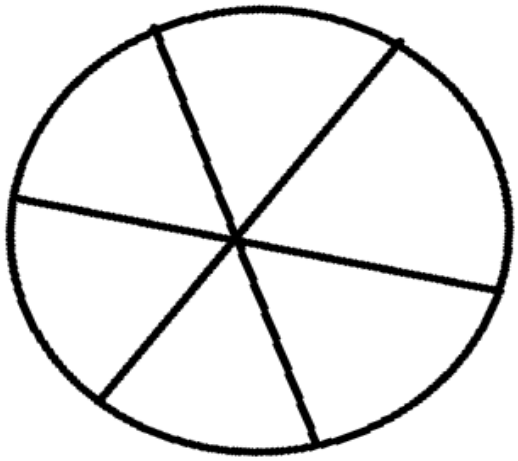
1. h = 2.4 cm
   d = 7.3 cm
   r = 3.7 cm



2. h = 2.5 cm
   d = 7.3 cm
   r = 3.7 cm



3. h = 2.2 cm
   d = 7 cm
   r = 3.5 cm



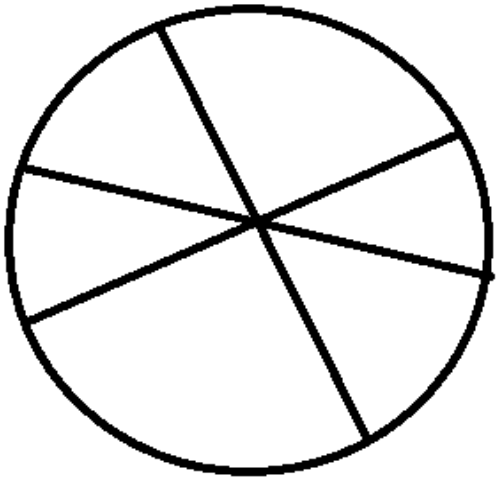
The Amlodipine Besylate powder is a **possible flow.** The acceptable range of Angle of Repose is 0 – 50 ˚ in my study Amlodipine Besylate Angle of Repose by funnel method is 33˚.02’ so this drug is suitable for direct compression by SeDeM.

Table No: 8.1 Angle of Repose of Amlodipine Besylate by Open End Cylinder Method

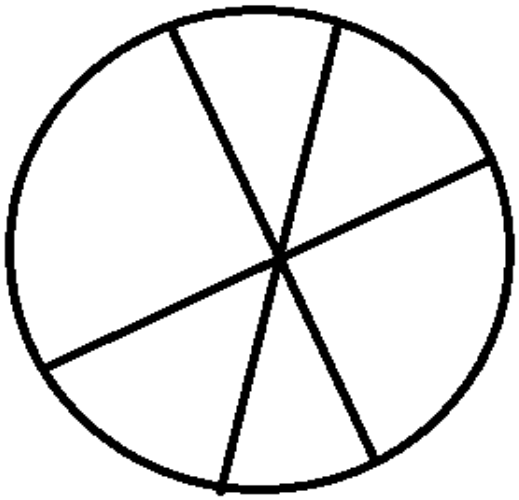
Name of the Drug Powder	Height of The Pile (h) cm	Diameter of The Pile (d) cm	Radius of the Pile (r) cm	h/r	$Q = \tan^{-1}$ (h/r)	Average
Amlodipine Besylate	2	6.1	3.1	0.64	32˚61’	
	2.1	6	3	0.7	34˚99’	34˚99’
	2.1	5.9	3	0.7	34˚99’	

ANGLE OF REPOSE OF AMLODIPINE BESYLATE DRUG BY OPEN END CYLINDER METHOD GRAPH:

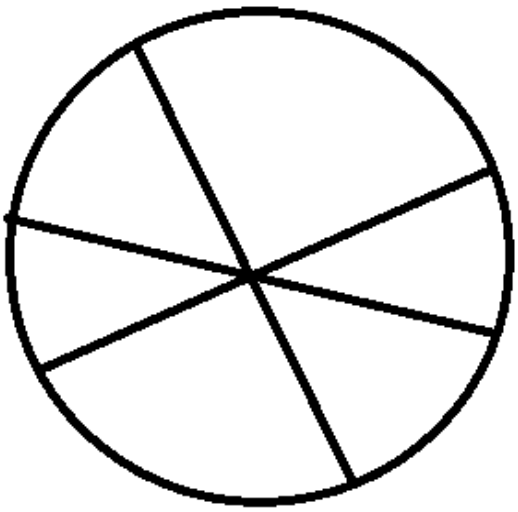
1. h = 2.5 cm
   d = 7.3 cm
   r = 3.7 cm



2. h = 2.2 cm
   d = 7.2 cm
   r = 3.6 cm



3. h = 2.2 cm
   d = 7.1 cm
   r = 3 cm



The AmlodipineBesylate powder is a **possible flow.** The acceptable range of Angle of Repose is 0 – 50 ˚ in my study Amlodipine Besylate Angle of Repose by open end cylinder method is 34˚99’ so this drug is suitable for direct compression by SeDeM.

Flowability (t″):

Open End Cylinder Method

Sample = Amlodipine Besylate

Table No: 8.2 Flowability of Amlodipine besylate by open end cylinder method

S.NO	PASSING TIME (Sec)
1.	3 sec
2.	4 sec
3.	2 sec

Average mean= (3+4+2)/3

= **3sec**

The acceptable range of Flow ability is 0 – 20sec in my study Amlodipine Besylate Flow ability is 3 sec so this drug is agreed to suitable for direct compression by SeDeM.

LOSS ON DRYING (%HR):

Loss on drying = Initial weight of the drug – Final weight of the drug X 100

= 10 – 9.78X 100

= 0.22 X 100

= **22%**

The acceptable range of loss on drying is 0 – 10(%)in my study Amlodipine Besylate loss on drying is 22%so this drug is may be suitable for direct compression by SeDeM.

HYGROSCOPICITY (%H):

Hygroscopicity = (Final weight of the drug – initial weight of the drug) X 100

= 10.19 -10

= 0.19 X 100

= **19%**

The acceptable range of hygroscopicity is 0 – 20% in my study Amlodipine Besylate hygroscopicity is 19% so this drug is possible to suitable for direct compression by SeDeM.

PARTICLE SIZE (% Pf) OF AMLODIPINE BESYLATE DRUG EYE PIECE MICROMETER:

CALIBRATION OF EYEPIECE MICROMETER:-

1 Division of stage micrometer = 0.01mm = 10 micron

$$1 \text{ Division of Eye-piece micrometer} = \frac{\text{No. of division of stage micrometer}}{\text{No. of division of Eye-piece Micrometer}} \times 10\mu$$

One division of eye piece micrometer = **12.5 µm**

Table No: 8.3 PARTICLE SIZE (% Pf) OF AMLODIPINE BESYLATE DRUG BY EYE PIECE MICROMETER:

S.NO	EYEPIECE DIVISION	PARTICLE SIZE (µm)	S.NO	EYEPIECE DIVISION	PARTICLE SIZE (µm)
1.	5	62.5	41.	6	75
2.	3	37.5	42.	2	25
3.	4	50	43.	3	37.5
4.	6	75	44.	3	37.5
5.	2	25	45.	2	25
6.	1	12.5	46.	2	25
7.	4	50	47.	1	12.5
8.	2	25	48.	6	75
9.	3	37.5	49.	6	62.5
10.	7	87.5	50.	5	62.5
11.	6	75	51.	4	50
12.	2	25	52.	2	25
13.	3	37.5	53.	3	37.5
14.	1	12.5	54.	4	50
15.	2	25	55.	5	62.5
16.	3	37.5	56.	6	75
17.	3	37.5	57.	1	12.5
18.	4	50	58.	2	25
19.	6	75	59.	3	37.5
20.	1	12.5	60.	5	62.5
21.	5	62.5	61.	4	50
22.	4	50	62.	4	50
23.	3	37.5	63.	4	50
24.	3	37.5	64.	6	75
25.	2	23	65.	7	87.5
26.	4	50	66.	4	50
27.	5	62.5	67.	3	37.5
28.	3	37.5	68.	2	25
29.	2	25	69.	1	12.5
30.	3	37.5	70.	6	75
31.	4	50	71.	5	12.5
32.	5	62.5	72.	4	50
33.	3	37.5	73.	4	50
34.	3	37.5	74.	3	37.5
35.	1	12.5	75.	2	25
36.	3	37.5	76.	1	12.5
37.	2	25	77.	2	25
38.	3	32.5	78.	2	25
39.	4	50	79.	3	37.5
40.	3	37.5	80.	4	50

S.NO	EYE PIECE DIVISION	PARTICLE SIZE (µm)	S.NO	EYE PIECE DIVISION	PARTICLE SIZE (µm)
81.	5	62.5	91.	3	37.5
82.	6	75	92.	3	37.5
83.	7	87.5	93.	4	50
84.	7	87.5	94.	5	62.5
85.	3	37.5	95.	2	25
86.	3	37.5	96.	6	75
87.	3	37.5	97.	7	87.5
88.	2	25	98.	2	25
89.	4	50	99.	3	37.5
90.	5	62.5	100.	4	50

Table No: 8.4 CALIBRATION OF AMLODIPINE BESYLATE

S.NO	AVERAGE SIZE	MIDPOINT	NO.OF PARTICLES PRESENT
1.	0-20	10	8
2.	20-40	30	47
3.	40-60	50	19
4.	60-80	70	21
5.	80-100	90	5

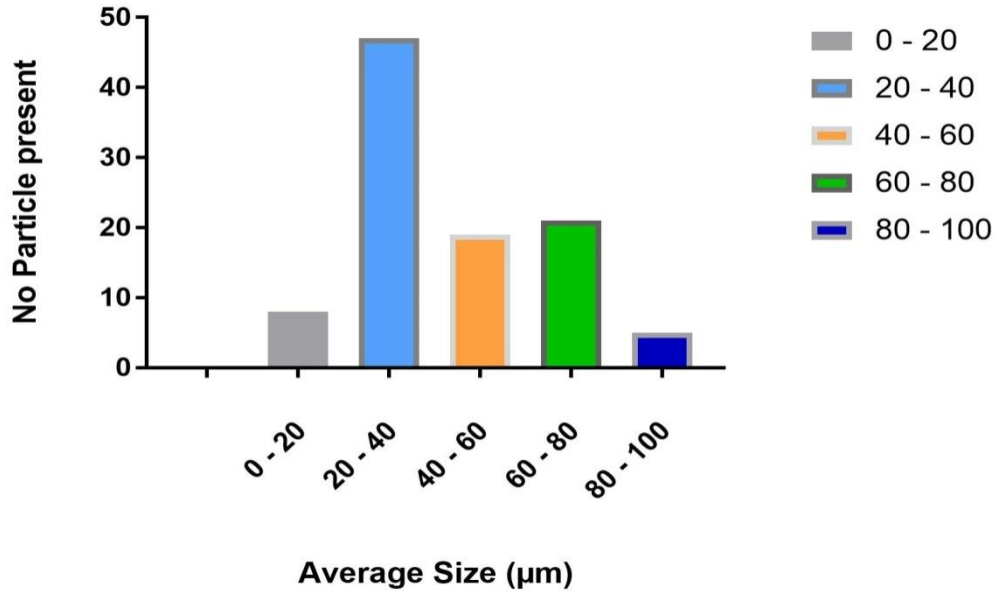


Figure: 8.4 PARTICLE SIZE DISTRIBUTION OF AMLODIPINE BESYLATE

The Amlodipine Besylate Average particle size is 44.5µ then it's particle mean diameter level is 44.5µ, and it's total number of size range is 0-100 µ and Amlodipine Besylate Size range of which maximum particle

exist is 20-40 µm and finally Mode diameter is 25 µ,37.5 µThe acceptable range of particle size is 50µ in my study Amlodipine Besylate particle size by eye piece micrometer is 44.5µ so this drug is suitable for direct compression by SeDeM.

Table No: 8.5DETERMINATION OF AMLODIPINE BESYLATE DRUG PARTICLE SIZE BY SIEVING METHOD:

S.NO	Sieve no	Sieve opening (µ)	Mean size opening (µ)	Weight of the Drug retain (gms)	Percentage weight of the Drug	Weight size
1.	80	177	177	0.67 x 10 = 6.7	6.7%	1185.9
2.	80/100	177/149	163	0.80 x 10 = 8	8%	1304
3.	100/120	149/125	211.5	1.05 x 10 = 10.5	10.5%	2220.75
4.	120	125	125	6.02 x 10 = 60.2	60.2%	7525
5.	Total Weight of the drug Percentage & Weigh Size				**85.4%**	**12235.65**

Weigh size = Arithmetic mean size of opening x percentage of weight of the powder obtained

$$\text{Arithmetic mean} = \frac{\text{Weigh size}}{100} = \frac{12235.65}{100} = 122.37\mu$$

Percentage under size (adding up to weight size)

Percentage oversize (From the 100 subtract the values)

Table No: 8.6AMLODIPINE BESYLATE DRUG PARTICLE SIZE BY SIEVING METHOD:

S.NO	Weight of Drug Retained (gm)	Particle Size Opening (μ)	Weight of Under Size	Weight of Oversize
1.	6.7	177	6.7	93.3
2.	8	163	14.7	85.3
3.	10.5	211.5	25.2	74.8
4.	60.2	125	85.4	14.6

The arithmetic mean of is Amlodipine Besylate**122.37μ**

HOMOGENEITY INDEX (Iθ):

$$I\theta = \frac{Fm}{100+(dm-dm-1)Fm-1+(dm+1-dm)Fm+1+(dm-dm-2)Fm-2+(dm+2-dm)Fm+2+(dm-dm-n)Fm-n+(dm+n-dm)Fm+n}$$

$$= \frac{22.21}{10287.001}$$

= 1.079%

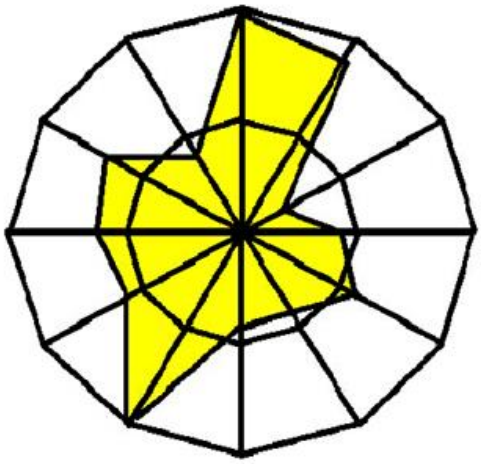
Table No: 8.7 HOMOGENEITY INDEX OF AMLODIPINE BESYLATE

Sieve (mm)	Corresponding	Average of the diameter of the fraction	Corresponding diameter (dm……dm± n)	Difference dm with the major component
0.177 – 0.250	Fm + 2	11.86	dm + 2	10.35
0.149 – 0.177	Fm + 1	13.04	dm + 1	9.17
0.125 – 0.149	Fm	22.21	dm	0
0.063 – 0.125	Fm – 1	75.25	dm - 1	53.04
<0.063	Fm – 2	0	dm – 2	22.21

Amlodipine Besylate homogeneity index 88.622**%** is so this drug may be suitable for direct compression by SeDeM.

Table No: 8.7A Sedem Method To API In Amlodipine Besylate Powder Form Calculation

INCIDENCE	PARAMETER	ACCEPTABLE RANGE	Radius(r)	Mean incidence
Dimension	Bulk density	0 - 1g/ml	3.1	3.8
	Tapped density	0 – 1g/ml	4.5	
Compressibility	Inter – particle porosity	0 – 1.2	8.073	6.80
	Carr index	0 – 50(%)	6.222	
	Cohesion index	0 – 200 (N)	6.1	
Flowability /powder flow	Hausner ratio	3 – 1	7.74	4.63
	Angle of repose	50 – 0 (0˚)	3.156	
	Power flow	20 – 0 (S)	3	
Lubricity/ Stability	Loss on drying	0 – 10(%)	12	6.53
	hygroscopicity	20 – 0 (%)	0.5	
Lubricity/dosage	Particles <50µ	50 – 0(%)	7.08	4.08
	Homogeneity index	0 – 2 X 10 – 2	1.080	
Parametric profile index (mean r of all parameters)			5.213	
Good compression index (IGC)			6.80	



- Dimension = 3.8
- Compressibility = 6.80
- Flowability /powder flow = 4.63
- Lubricity/ Stability = 6.53

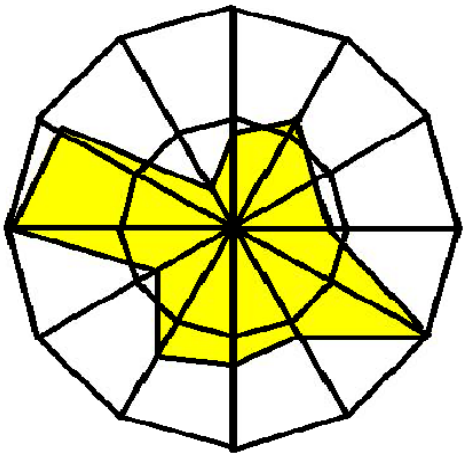


Figure: 8.7A Sedem Diagram Of Amlodipine Besylate Formulation

Parametric profile index = 5.68

Good compression index (IGC) = 6.44

Evaluation of the Amlodipine Besylate Tablet

Weight Variation:

$$\% \text{ Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

= 3.02/20

Aveage weight = **0.151mg**

Table No: 8.7B Weight Variation of the Amlodipine Besylate Tablet

S.No	Tablet Weight	% Deviation
1.	0.15	100
2.	0.15	100
3.	0.16	104.8
4.	0.15	100
5.	0.15	100
6.	0.16	104.8
7.	0.15	100
8.	0.16	104.8
9.	0.15	100
10.	0.15	100
11.	0.14	96.7
12.	0.15	100
13.	0.16	104.8
14.	0.14	96.7
15.	0.15	100
16.	0.15	100
17.	0.15	100
18.	0.15	100
19.	0.15	100
20.	0.15	100

Friability:

$$\text{\% Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Initial wt.of tablet (20) = 3.02g

Weighed of 20 tablet after friabilation = 2.07g

Wt.loss =3 02-2.76

= 0.26g

Hardness:

Table No: 8.7C Hardness of the Amlodipine Besylate Tablet

S.No	Hardness kg/cm^2
1.	1.2
2.	1.2
3.	1.6
4.	1.4
5.	1.2
6.	1.4
7.	1.6
8.	1.6
9.	1.2
10.	1.2

Average hardness = 1.22kg/cm^2

Table No: 8.7d Dissolution of the Amlodipine Besylate Tablet

S.No	Time(min)	Absorbance	% Drug release
1.	5	0.039	59.76
2.	10	0.042	64.26
3.	15	0.045	68.94
4.	20	0.049	75.06
5.	25	0.054	82.62
6.	30	0.055	84.24

OLMESARTAN MEDOXOMIL:

Bulk Density (Da):

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of the powder}}{\text{Bulk volume}}$$

$$= \frac{10}{19}$$

= **0.53 gm/ml**

The acceptable range of Bulk density is 0 - 1g/ml in my study Olmesartan Medoxomil bulk density range is 0.53 gm/ml so this drug is made suitable for direct compression by SeDeM

Tapped density (Dc):

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume}}$$

$$= \frac{10}{13}$$

= **0.77gm/ml**

The acceptable range of Tapped density is 0 – 1g/ml in study Olmesartan Medoxomil Tapped density range is 0.77gm/ml so this drug is allowed suitable for direct compression by SeDeM

Average bulk density:

$$\text{Average bulk density} = \frac{Da + Dc}{2}$$

$$= \frac{0.53 + 0.77}{2}$$

= **0.65 gm/ml**

Inter Particle Porosity (Ie):

$$\text{Inter particle Porosity} = 1 - \left[\frac{Da}{Dc}\right]$$

= 1 – (0.53/0.77)

Porosity = 1- 0.6883

= **0.3117**

The acceptable range of Inter Particle Porosity is 0 – 1.2 in my study Olmesartan Medoxomil Inter Particle Porosity range is 0.3117 so this drug is suitable for direct compression by SeDeM

Carr's Index (Ic):

$$Ic = \frac{(Dc - Da)}{Dc} \times 100$$

$$= \frac{0.77 - 0.53}{0.77} \times 100$$

$$=0.3116883 \times 100$$

= **31.168%**

The acceptable range of Carr Index is 0 – 50 % in my study Olmesartan Medoxomil Carr Index range is 31.168% so this drug is passible to suitable for direct compression by SeDeM.

Cohesion Index (Icd):

The acceptable range of Cohesion Index is 0 – 200N Olmesartan Medoxomil Cohesion Index is 1N. It allows the drug formulate suitable for direct compression by SeDeM.

Hausner's ratio:

$$\text{Hausner's ratio (IH)} = \frac{Dc}{Da}$$

$$= \frac{0.77}{0.53}$$

= **1.452**

When t is the tapped density and d is bulk density. Lower H(<1.25) indicates better flow properties than higher ones(>1.25). The acceptable range of Hausner's ratio is 1 – 3 in my study Olmesartan Medoxomil Hausner's ratio is 1.452 hence, this drug is made suitable for direct compression by SeDeM.

Angle of Repose (θ)

$\tan\theta = h/r \quad \theta = \tan^{-1}(h/r)$

Table No: 8.8 ANGLE OF REPOSE OF OLMESARTAN MEDOXOMIL DRUG BY FUNNEL METHOD

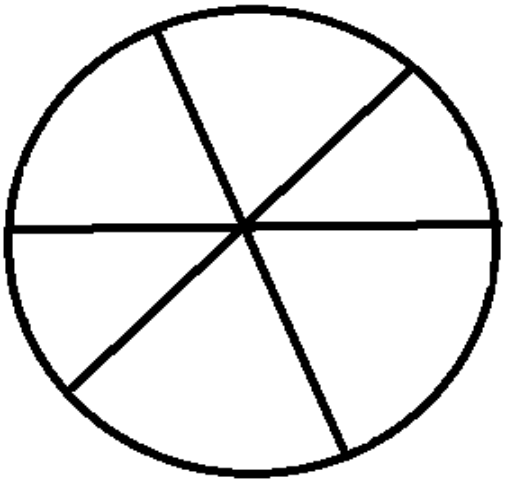
Name of the drug powder	Height of the pile (h) cm	Diameter of the pile (d) cm	Radius of the pile (r) cm	h/r	Q= $\tan^{-1}$ (h/r)	Average
Olmesartan Medoxomil	2.2	5.8	2.9	0.76	37˚.23'	
	2.1	6	3	0.7	34˚.99'	34˚.99'
	2.2	5.9	3	0.73	36˚.12'	

ANGLE OF REPOSE OF OLMESARTAN MEDOXOMIL DRUG BY FUNNEL METHOD GRAPH:

1. h = 2.2 cm

   d = 5.8 cm

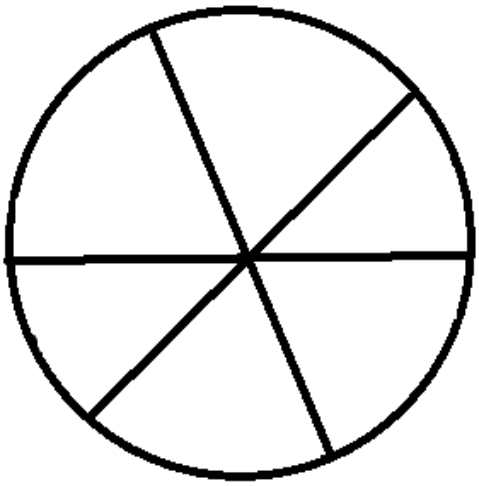
   r = 2.9 cm



2. h = 2.1 cm

   d = 6 cm

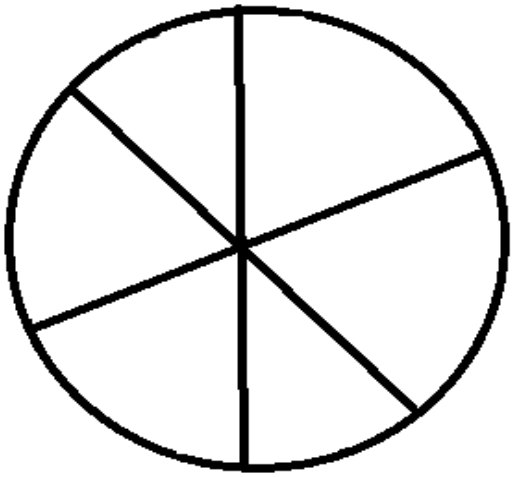
   r = 3 cm



3. h = 2.2 cm

   d = 5.9 cm

   r = 3 cm



The Olmesartan Medoxomil powder is a **possible flow.** The acceptable range of Angle of Repose is 0 – 50 ˚ in my study Olmesartan Medoxomil powder Angle of Repose by funnel method is 34˚.99’ so this drug is suitable for direct compression by SeDeM.

OPEN END CYLINDER TECHNIQUES:

Table No: 8.9Angle of Repose of Olmesartan Medoxomil Drug By Open End Cylinder Method

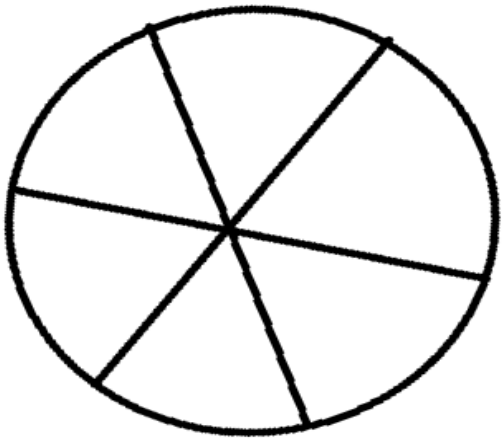
Name of the drug powder	Height of the pile (h) cm	Diameter of the pile (d) cm	Radius of the pile (r) cm	h/r	$\Theta = \tan^{-1}$ (h/r)	Average
Olmesartan medoxomil	2	6.1	3.1	0.64	32˚.61’	34˚.99’
	2.1	6	3	0.7	34˚.99’	
	2.1	5.9	3	0.7	34˚.99’	

ANGLE OF REPOSE OF OLMESARTAN MEDOXOMIL DRUG OPEN END CYLINDER METHOD GRAPH:

1. h = 2 cm

   d = 6.1 cm

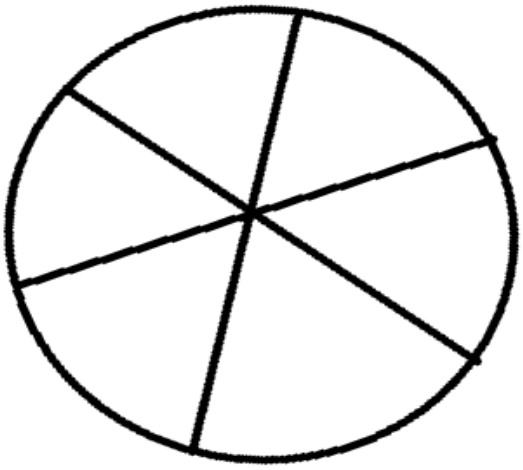
   r = 3.1 cm



2. h = 2.1 cm

   d = 6 cm

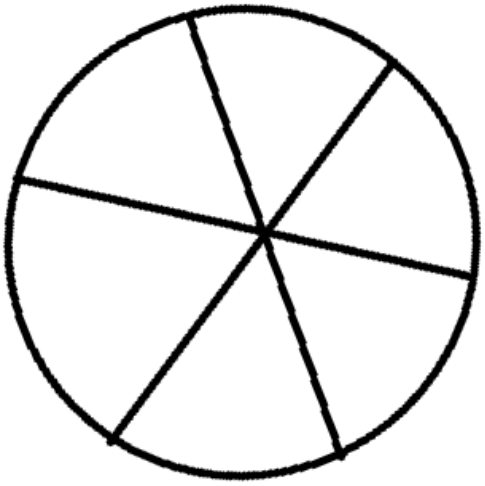
   r = 3 cm



3. h = 2.1 cm

   d = 5.9 cm

   r = 3 cm



The Olmesartan Medoxomil drug is a **possible flow.** The acceptable range of Angle of Repose is 0 – 50 ˚ in my study Olmesartan Medoxomil drug Angle of Repose by open end cylinder method is 34˚.99’ so this drug is potentially suitable for direct compression by SeDeM.

Flowability (t″)

Open End Cylinder Method

Sample = Olmesartan Medoxomil

Table: 8.10 Flow Ability of Olmesartan Medoxomil Drug Using Open End Cylinder Method

S.NO	PASSING TIME (Sec)
1.	2 sec
2.	3 sec
3.	2 sec

Average mean = (2+3+2)/3 x 10

= **3.5sec**

The acceptable range of Flowability is 0 – 20sec in my study Olmesartan Medoxomil Flowability is 3.5sec so this drug is suitable for direct compression by SeDeM.

LOSS ON DRYING:

Loss on drying = Initial weight of the drug – Final weight of the drug X 100

= 10 – 9.83 X 100

= 0.17 X 100

= 17%

The acceptable range of loss on drying is 0 – 10(%) in the present study Olmesartan Medoxomil loss on drying is 17%, as a result, this drug is may be suitable for direct compression by SeDeM.

HYGROSCOPICITY (%H):

Hygroscopicity = (Final weight of the drug – initial weight of the drug) X 100

= 10.12 -10 X 100

= 0.12 X 100

= **12%**

The acceptable range of hygroscopicity is 0 – 20% in my study Olmesartan Medoxomil hygroscopicity is 12% so this drug is fitting for direct compression by SeDeM.

Particle Size (%Pf) Of Olmesartan Medoxomil Drug by Eye Piece Micrometer

Calibration Of Eye Piece Micrometer:-

$$\text{One division of Eyepiece micrometer} = \frac{\text{No of division of stage micrometer}}{\text{No of division of eye – piece micrometer}} \times 10\mu$$

1. 5/4 x 10 = 12.5
2. 10/8 x 10 = 12.5
3. 15/12 x 10 = 12.5

One division of eyepiece micrometer = 12.5 µm

Table N0:8.11 Particle Size of Olmesartan Medoxomil by Eye Piece Micrometer

S.NO	EYE PIECE DIVISION	PARTICLE SIZE (µm)	S.NO	EYE PIECE DIVISION	PARTICLE SIZE (µm)
1.	8	100	41.	14	175
2.	10	125	42.	13	162.5
3.	12	150	43.	12	150
4.	8	100	44.	14	175
5.	9	112.5	45.	13	162.5
6.	11	137.5	46.	12	150
7.	15	187.5	47.	11	137.5
8.	12	150	48.	14	175
9.	12	150	49.	15	187.5
10.	15	187.5	50.	15	187.5
11.	13	162.5	51.	15	187.5
12.	18	225	52.	15	187.5
13.	12	150	53.	14	175
14.	15	187.5	54.	11	137.5
15.	13	162.5	55.	12	150
16.	15	187.5	56.	13	162.5
17.	11	137.5	57.	14	175
18.	16	200	58.	11	137.5
19.	12	150	59.	11	137.5
20.	17	212.5	60.	12	150
21.	11	137.5	61.	15	187.5
22.	14	175	62.	16	200
23.	12	150	63.	14	175
24.	15	187.5	64.	15	187.5
25.	11	137.5	65.	11	137.5
26.	11	137.5	66.	15	187.5
27.	11	137.5	67.	13	162.5
28.	12	150	68.	14	175
29.	15	187.5	69.	11	137.5
30.	16	200	70.	14	175
31.	14	175	71.	13	162.5
32.	12	150	72.	12	150
33.	13	162.5	73.	14	175
34.	14	175	74.	8	100
35.	11	137.5	75.	10	125
36.	15	187.5	76.	12	150
37.	13	162.5	77.	8	100
38.	15	187.5	78.	9	112.5
39.	11	137.5	79.	11	137.5
40.	15	187.5	80.	15	187.5

S.NO	EYE PIECE DIVISION	PARTICLE SIZE (µm)	S.NO	EYE PIECE DIVISION	PARTICLE SIZE (µm)
81.	12	187.5	91.	16	137.5
82.	12	150	92.	12	200
83.	15	150	93.	17	150
84.	13	187.5	94.	11	212.5
85.	18	162.5	95.	14	137.5
86.	12	225	96.	12	175
87.	15	150	97.	15	150
88.	13	187.5	98.	11	187.5
89.	15	162.5	99.	15	137.5
90.	11	187.5	100.	11	187.5

Table No: 8.12 particles Size of Olmesartan Medoxomil

S.NO	AVERAGE SIZE	MIDPOINT	NO.OF PARTICLES PRESENT
1.	0 – 50	25	-
2.	50 – 100	75	4
3.	100 – 150	175	42
4.	150 – 200	175	50
5.	200 – 250	225	4
6.	250 – 300	275	-

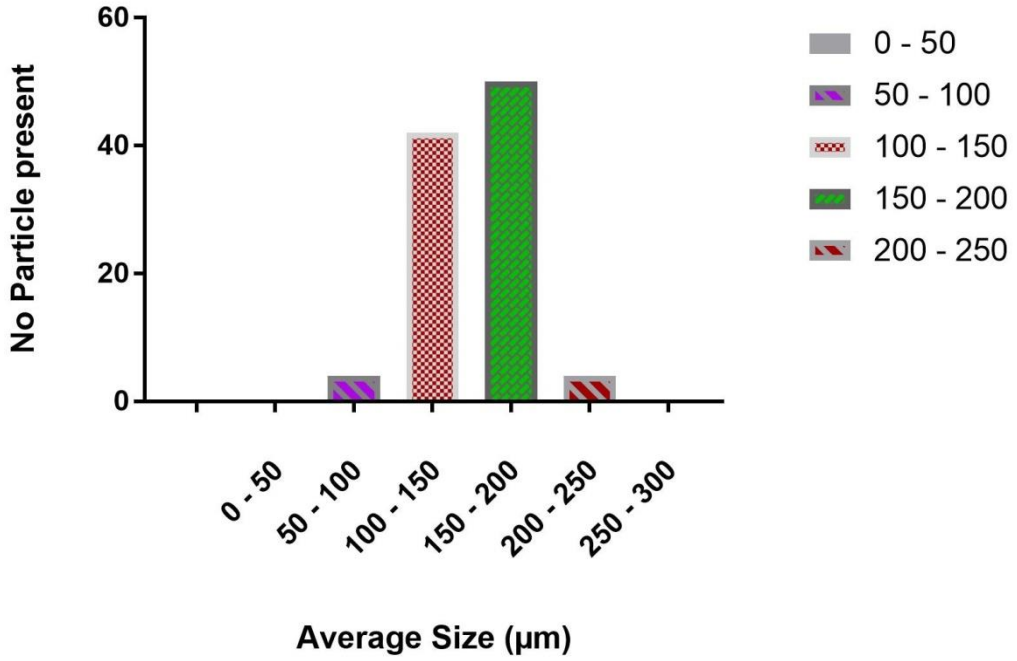


Figure No: 8.12 PARTICLE SIZE DISTRIBUTION OF OLMESARTAN MEDOXOMIL

The Average Olmesartan Medoxomil particle size is160.5µm, and my study drug particle mean diameter is 160.5µm, with Total range is 0-300µ and Size range of which maximum particle exist is 150-200µm with Mode diameter of 175µ, 187.5µ, 162.5µ, 200µ.The acceptable range of particle size is 50µ in my study Olmesartan Medoxomil particle size by eye piece micrometer is 160.5µso this drug may be suitable for direct compression by SeDeM.

Table No: 8.13 Determination of Olmesartan Medoxomil Drug Particle Size by Sieving Method

S.NO	Sieve no	Sieve opening (µ)	Mean size opening (µ)	Weight of the Drug retain (gms)	Percentage weight of the Drug	Weight size
1.	44	355	355	0.52 x 10 = 5.2	5.2%	846
2.	44/60	355/250	302.5	0.95 x 10 = 9.5	9.5%	2873.75
3.	60/80	250/177	213.5	1.85 x 10 = 18.5	18.5%	3949.75
4.	80	177	177	6.51 x 10 = 65.1	65.1 %	11522.7
5.	Total Weight of the Drug Percentage & Weigh Size				**98.3%**	**191.922**

Weigh size = Arithmetic mean size of opening x percentage of weight of the powder obtained

$$\text{Arithmetic mean} = \frac{\text{Weigh size}}{100} = \frac{19192.2}{100} = 191.922\mu$$

Percentage under size (adding up to weight size)

Percentage oversize (From the 100 subtract the values)

TABLE No: 8.14 OLMESARTAN MEDOXOMIL DRUG PARTICLE SIZE BY SIEVING METHOD

S.NO	WEIGHT OF DRUG RETAINED (gm)	PARTICLE SIZE OPENING (μ)	WEIGHT OF UNDER SIZE	WEIGHT OF OVERSIZE
1.	5.2	355	5.2	94.80
2.	9.5	302.5	14.7	85.3
3.	18.5	213.5	33.2	66.8
4.	65.1	177	98.3	1.7

The arithmetic mean of olmesartan Medoxomil is **191.922μ**

HOMOGENEITYINDEX (Iθ):

$$I\theta = \frac{Fm}{100+(dm-dm-1)Fm-1+(dm+1-dm)Fm+1+(dm-dm-2)Fm-2+(dm+2-dm)Fm+2 +(dm-dm-n)Fm-n+(dm+n-dm)Fm+n}$$

$$= \frac{39.50}{21003.61}$$

$$=0.001880629\%$$

Table No: 8.15 Homogeneity Index of Olmesartan Medoxomil

Sieve (mm)	Corresponding	Average of the diameter of the fraction	Corresponding diameter (dm……dm± n)	Difference dm with the major component
0.355 – 0.850	Fm + 2	18.46	dm + 2	21.04
0.250 – 0.355	Fm + 1	28.74	dm + 1	10.76
0.177 – 0.250	Fm	39.50	dm	0
0.149 – 0.177	Fm – 1	115.22	dm – 1	75.72
<0.149	Fm – 2	0	dm – 2	39.5

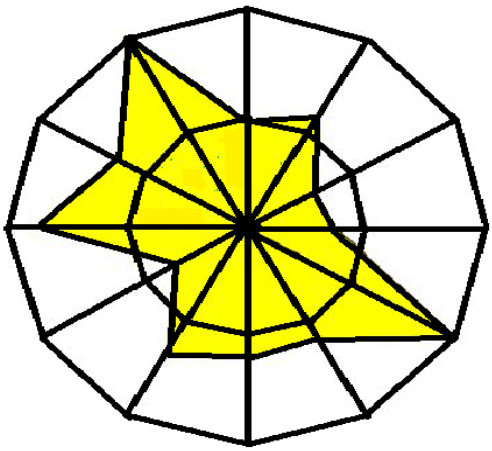
Olmesartanmedoxomil homogeneity index158.395**%** is, therefore, this drug may be suitable for direct compression by SeDeM.

Table No: 8.16 Olmesartan Medoxomil and Amlodipine Besylate Compared To Acceptable Range

INCIDENCE	PARAMETER	ACCEPTABLE RANGE	OLMESARTAN MEDOXOMIL	AMLODIPINE BESYLATE
Dimension	Bulk density	0 - 1g/ml	0.53 g/ml	0.3 g/ml
	Tapped density	0 – 1g/ml	0.77 g/ml	0.45g/ml
Compressibility	Inter – particle porosity	0 – 1.2	0.3111 gm/ml	0.312gm/ml
	Carr index	0 – 50(%)	31.17%	31.11%
	Cohesion index	0 – 200 (N)	1.22N	1N
Flowability /powder flow	Hausner ratio	3 – 1	1.452	1.451
	Angle of repose	50 – 0 (0˚)	34˚ 99’	34˚99’
	Power flow	20 – 0 (S)	3.5sec	3 sec
Lubricity/ Stability	Loss on drying	0 – 10(%)	17%	22%
	higroscopicity	20 – 0 (%)	12%	19%
Lubricity/dosage	Particles <50µ	50 – 0(%)	98.3%	85.4%
	Homogeneity index	0 – 2 X 10 – 2	88.622	158.395

Table No: 8.17 Sedem Method to API in Olmesartan Medoxomil Drug Form Calculation

INCIDENCE	PARAMETER	ACCEPTABLE RANGE	Radius(r)	Mean incidence
Dimension	Bulk density	0 - 1g/ml	5.3	6.5
	Tapped density	0 – 1g/ml	7.7	
Compressibility	Inter – particle porosity	0 – 1.2	8.074	6.436
	Carr index	0 – 50(%)	6.234	
	Cohesion index	0 – 200 (N)	5	
Flowability /powder flow	Hausner ratio	3 – 1	7.76	4.754
	Angle of repose	50 – 0 (0˚)	3.002	
	Power flow	20 – 0 (S)	3.5	
Lubricity/ Stability	Loss on drying	0 – 10(%)	7	5.5
	higroscopicity	20 – 0 (%)	4	
Lubricity/dosage	Particles <50µ	50 – 0(%)	9.66	5.30
	Homogeneity index	0 – 2 X 10 – 2	0.940	
Parametric profile index (mean r of all parameters)			5.68	
Good compression index (IGC)			6.44	



- Dimension = 6.5
- Compressibility = 6.436
- Flow ability /powder flow = 4.754
- Lubricity/ Stability = 5.5

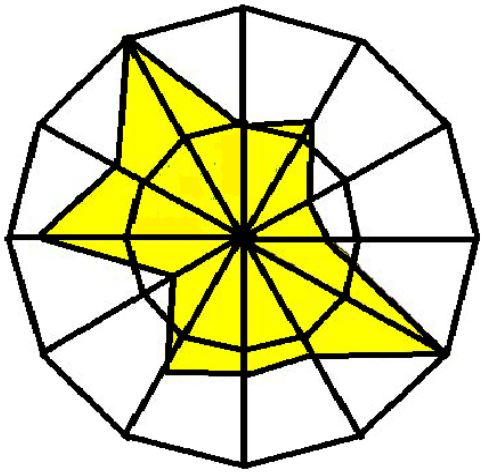


Figure: 8.17 SeDeM diagram of olmesartan medoxomil formulation

Parametric profile index = 5.68

Good compression index (IGC) = 6.44

Evaluation of the Olmesartan Medoxomil Tablet

Weight Variation:

$$\text{\% Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

= 3.12/20

Average weight = **0.156mg**

Table No: 8.18 Weight Variation of the Olmesartan Medoxomil Tablet

S.No	Tablet Weight	% Deviation
1.	0.15	100
2.	0.16	104
3.	0.13	92
4.	0.16	104
5.	0.16	104
6.	0.16	104
7.	0.15	100
8.	0.16	104
9.	0.16	104
10.	0.16	104
11.	0.16	104
12.	0.16	104
13.	0.15	100
14.	0.15	100
15.	0.15	100
16.	0.16	104
17.	0.15	100
18.	0.17	108
19.	0.17	108
20.	0.15	104

Friability:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Initial wt.of Tablet(20) =3.15g

Weighed of 20 tablet after friabilation =2.95g

Wt.loss =3.15-2.95

=0.2g

Hardness:

Table No: 8.18 Hardness of the Olmesartan Medoxomil Tablet

S.No	Hardness kg/cm^2
1.	1
2.	1.4
3.	1
4.	1.2
5.	1
6.	1.4
7.	1.2
8.	1
9.	1.2
10.	1

Average hardness = 1kg/cm^2

Table No: 8.19 Dissolution Of The Olmesartan Medoxomil Tablet.

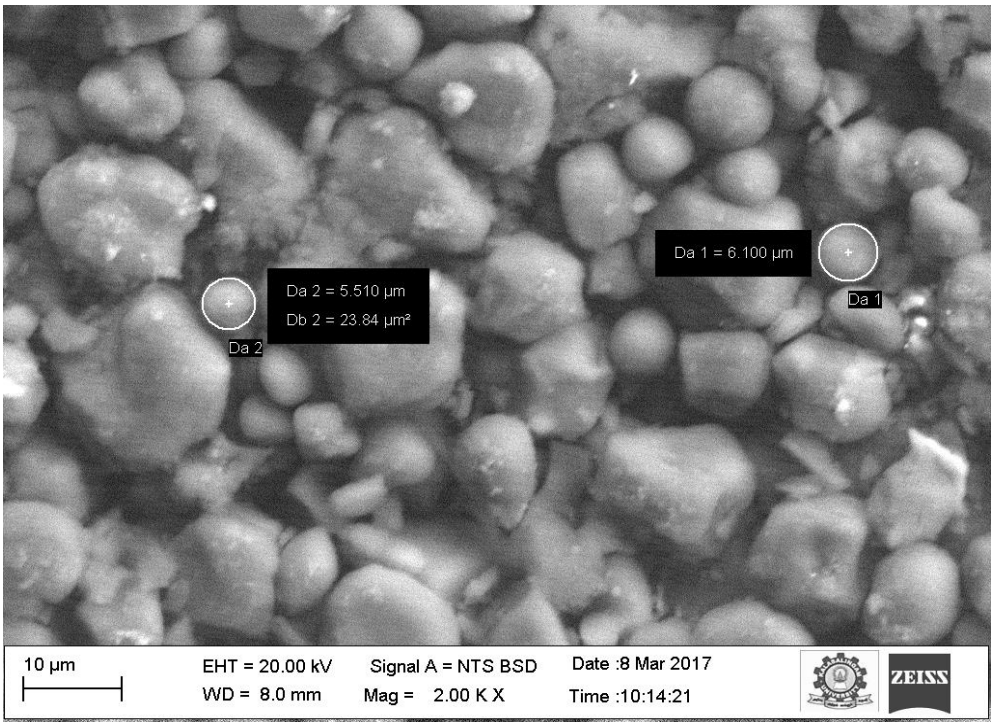
S.No	Time(min)	Absorbance	% Drug Release
1.	5	0.207	51.84
2.	10	0.211	52.92
3.	15	0.218	54.63
4.	20	0.221	55.35
5.	25	0.228	57.15
6.	30	0.236	59.13

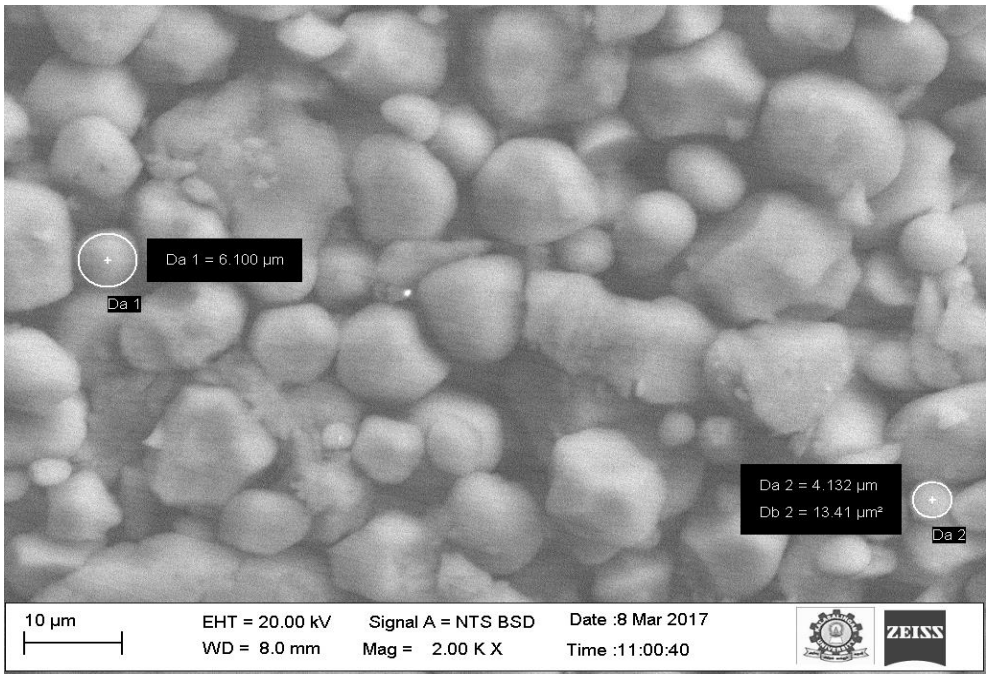
Scanning Electron Microscopy (olmesartan Medoxomil and Amlodipine Besylate)

The morphological appearance of the electrospun fiber and that fiber were investigated by a ZEISS-5200 scanning electron microscope (SEM), operating at an acceleration voltage of 20 KV. For each sample, the average diameter of the individual fibers was measured from multiple SEM images at the magnification of 2.0 KX by semaphore 4.0 software. The result of each sample was reported as an average value from at least three measurements. A Lloyd LRX universal tester was used to determine the mechanical integrity of some of the as-spun fibers. The gauge length and the crosshead speed were 10 µm per minute, respectively.

The percentage of particle size is measured generally in sieving method according to the pharmacopeial standard requirement, but I was trying to measure the particle size and distribution of particle size in within the tablet as using SEM. These are accurate measure method for the particle size analysis. According to SEM method results found out the <10µm particles present in the prepared tablet, that was a very crucial factor for sedem diagram direct compression method. This result gave the precious result of homogeneity index, this index was an important factor for during drug disintegration and dissolution of tablet dosage form in this method of manufacturing. The amlodipine Besylate tablet drug and excipient particle size distribution is 5.5µm which gives the theoretical QBD designing conclusion and has been giving significant dissolution of tablet and the same thing also of olmesartan Medoxomil tablet. So from this SEM results, these prepared tablets were fulfilled the

sedem diagram one of a parameter of particle size and homogeneity. The particles are also having lubricity energy, because they under processing of direct compression lubricity values has been detected, which results in poor particle size distribution, weight variation, and content uniformity of tablet dosage form. The above parameters are results to below the compendial limit which is the dosage forms has been unqualified for the human use, so from this results in these prepared tablets meet the compendia level for IP 2016.




Da 1 = 6.100 µm
Da 1
Da 2 = 4.132 µm
Db 2 = 13.41 µm²
Da 2
10 µm
EHT = 20.00 kV
WD = 8.0 mm
Signal A = NTS BSD
Mag = 2.00 K X
Date :8 Mar 2017
Time :11:00:40
ZEISS


Conclusion

CONCLUSION

Now we developed a unique methodology for the preformulation and powder substance description. This process facilitates a study on the design and development of formulations for the manufacture of tablets by direct compression. The SeDeM specialist method is a helpful tool since, in adding up to allow for the type of mechanism, it also provide a recommendation on the intrinsic property, such as the character and morphology of the particles. We recommend that given the correctness of the in sequence provide by this method, formulations determination have a higher possibility of successfully compressed. This method characterizes the individual mechanism of a formulation and applies a mathematical testing to find out the accurate amount of both in the finishing formulation. The formulation provides will be suitable for direct compression. This modern method offers various advantages from a production view. In adding to creature faster than other technique, it is necessary as it reduces the number of steps at some stage in the manufacturing process., SeDeM has the benefit of providing a formulation with the least amount of excipients as it combine the API by only one excipient and the standard formula of, consequently avoiding the used of unnecessary excipients, such as diluents, binder, and agglutinants. The information given by the SeDeM system contributes to an excellence by Design Development. Subsequently, this new tool is steady with the current requirements of narrow health establishment such as the FDA and ICH.

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